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(54) **MODIFIED RELEASE MULTIPLE-UNITS COMPOSITIONS OF NON-STEROID ANTI-INFLAMMATORY DRUG SUBSTANCES (NSAIDs)**

AUS MEHREREN EINZELEINHEITEN ZUSAMMENGESETZTE ARZNEIMITTEL MIT NICHT-STEROIDALEN WIRKSTOFFEN (NSAIDS)

COMPOSITIONS CONTENANT DES UNITES MULTIPLES A LIBERATION MODIFIEE DE SUBSTANCES MEDICAMENTEUSES ANTI-INFLAMMATOIRES NON STEROIDES (NSAID)

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Description

[0001] The present invention relates to an oral pharmaceutical modified release multiple-units composition for the administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance (in the following abbreviated "an NSAID substance") to obtain both a relatively fast or quick onset of the therapeutic effect and the maintenance of a therapeutically active plasma concentration for a relatively long period of time. The modified release multiple-units composition comprises at least two fractions of multiple units such as a first and a second fraction. The first fraction comprises individual units which are designed to quickly release the drug substance and the second fraction comprises individual units which are designed to slowly release the drug substance to enable a delayed and extended release of the drug substance. Typically, the second fraction comprises multiple units which are coated with a sustained release coating designed to release the drug substance in such a manner that the maintenance of a therapeutically active plasma concentration for a relatively long period of time are obtained. By suitable adjustment of the release pattern of the at least first and second fraction a composition is obtained which is adapted to once- or twice-a-day administration.

TECHNICAL BACKGROUND

[0002] Drug levels can be maintained above the lower level of the therapeutic plasma concentration for longer periods of time by giving larger doses of conventionally formulated dosage forms. However, it is not a suitable approach to increase dosage as such doses may produce toxic and undesired high drug levels. Alternatively, another approach is to administer a drug at certain intervals of time, resulting in oscillating drug levels, the so-called peak and valley effect. This approach is generally associated with several potential problems, such as a large peak (toxic effect) and valley (non-active drug level) effect, and a lack of patient compliance leading to drug therapy inefficiency or failure. If, however, the plasma concentration is kept constant over the therapeutic level using conventional tablets, an unacceptably high daily dosage is required if the active substance is not administered very frequently.

[0003] Controlled release compositions are known which are designed to rapidly release a fraction of a total drug dose. This loading dose is an amount of a drug which will provide a desired pharmacological response as fast as possible according to the biopharmaceutical properties of the drug substance. Generally, such compositions in some more or less sophisticated manner are composed of a sustained release part and a part which either contains a free amount of the drug substance or it releases the drug substance in the same manner as if the drug substance had been formulated as a plain formulation (e.g. in the form of normal tablets or granulates). Such compositions which initially release a burst of a therapeutic agent and then release the agent at an essentially constant rate are described, e.g., in WO 95/14460 (Euroceltique S.A.) published on 1 June 1995. The composition described therein relates to a sustained release opioid formulation comprising a plurality of substrates comprising the active ingredient in a sustained release matrix or coated with a sustained release coating comprising a retardant material. The sustained release beads are then coated with an opioid in immediate release form or, in the case the composition is in the form of a gelatine capsule, an amount of free opioid (i.e. the opioid is included as such and has not been processed into a specific formulation e. g. by means of pharmaceutically acceptable excipients) is incorporated into the gelatin capsule via inclusion of a sufficient amount of opioid within the capsule. In a further alternative, the gelatine capsule itself is coated with an immediate release layer of the opioid.

[0004] Generally, the rationale which lies behind the kind of compositions which have been described to enable an immediate release of a drug substance as well as a sustained release of the drug substance is to combine a traditional formulation approach (such as, e.g., i) plain tablets which have a disintegration time in water of at the most about 15 min for uncoated tablets, cf. Ph. Eur. (the requirements for coated tablets or capsules are at the most 30 min), ii) a traditionally formulated granulate or iii) loose powder of the drug substance itself) with a controlled release approach. By doing so the immediate release part of the composition is intended to release the drug substance in a manner which corresponds to a plain tablet formulation or the like and the term "immediate" is in such a context intended to denote that the release of the drug substance is faster than the release from a sustained release composition. The immediate release is in no way intended to be faster than that of a traditional or plain composition.

[0005] Especially in those cases where the drug substance has a low solubility in an acidic medium having a pH of from about 1 to about 3, i.e. a pH corresponding to the pH in the stomach, the traditional formulation approach will lead to a pharmaceutical composition which has a suitable fast disintegration time but not necessarily a suitable dissolution rate of the drug substance under acidic conditions, i.e. a plain tablet will rapidly disintegrate into granules but the dissolution of the drug substance from the composition and/or the disintegrated composition under acidic conditions may be unsuitable low due to the solubility properties of the drug substance itself. The availability of a drug substance with respect to absorption, i.e. entrance into the circulatory system, is dependant on the presence of the drug substance on dissolved form as it is generally accepted that only dissolved substances are capable of passing the mucous membranes in the gastro-intestinal tract. Therefore, it is important that the dissolution of the drug substance is suitably fast

even under acidic conditions in order to enable an initial absorption already from the stomach so that a true fast or immediate therapeutic response is obtainable. Furthermore, if a drug substance - dependant on pH - can exist on un-ionized as well as ionized form (e.g. acetyl salicylic acid which at an acid pH below its pK_a value predominantly is present on an unloaded, i.e. un-ionized form, whereas at a pH above its pK_a value predominantly is present on ionized form). For drug substances which are weak acids it is very important to ensure a proper bioavailability of the drug substance already under acidic conditions in order to achieve a true rapid therapeutic effect. However, the various approaches disclosed with respect to achievement of a combination of a rapid and a sustained effect (e.g. in the publications mentioned above) do not seem to take the above-mentioned factors into account and, hence, there is a need for developing compositions which enable a true rapid onset of the therapeutic effect as well as a sustained effect. To this end, we have especially focused on compositions comprising a drug substance suitable for use in situations where a rapid effect is needed but also in situations where an extended effect is desirable in order to develop compositions suitable for administration less frequent than compositions on the market today, more specifically to enable administration on a once or twice daily basis. Examples of suitable drug substances are, e.g., substances which have a pain relief effect. More specifically, interesting drug substances are those belonging to the class of drug substances normally denoted NSAIDs or NSAID substances.

[0006] In EP-A-0 438 249A1 (ELAN Corporation P.L.C.) is given another example of a composition which has been designed to release naproxen immediately and sustained. However, as shown in Example 18 herein, the so-called immediate release of naproxen does not take place under acidic conditions, i.e. conditions prevailing in the stomach. Accordingly, such a composition is not within the scope of the present application.

[0007] As will be apparent from the following the present inventors have developed a composition in multiple-units form for a quick release as well and an delayed and extended release.

[0008] Multiple-units formulation techniques according to the invention aim at a modified release of a drug substance in a predetermined pattern to control the peak plasma concentration without affecting the bioavailability, i.e. the extent of drug availability. The release of an NSAID substance from a composition according to the present invention is controlled in a very flexible manner as described below. Many advantages are obtained, e.g., the frequency of undesirable side effects may be reduced, and due to the control of the time it takes to obtain the peak plasma concentration and the prolongation of the time at the therapeutically active plasma concentration, the frequency of the administration may be reduced to a dosage taken only twice or once a day. This also serves to improve patient compliance. A further advantage of the modified release multiple-units dosage form is that high local concentrations of the active substance in the gastro-intestinal system are avoided, due to the units being distributed freely throughout the gastrointestinal tract, independent of gastric emptying.

[0009] Moreover, patients suffering from pain and/or inflammatory conditions and/or related conditions very often require high daily dosages of NSAID substances. If such high dosage of an NSAID substance should be given only once a day, the release from the dosage form must be safe, predictable and reliable. The composition should also be very storage stable because an immediate release due to accidental damaging of e.g. the coating or capsule of a high dosage form may result in undesired high plasma concentrations, so-called dose dumping, which could cause undesired side effects. Furthermore, from a technical point of view, the release rate and the release pattern of the active drug substance from the composition should not significantly change during the shelf-life of the composition. Even a minor change in the release rate and/or release pattern may have a significant impact on the *in vivo* performance of the composition.

[0010] By use of a coated multiple unit dosage form, the risk of dose dumping due to e.g. rupturing of a coating is reduced because the amount of active ingredient in each coated unit is negligible.

[0011] The compositions according to the present invention are intended to reduce or essentially eliminate problems identified with other kind of compositions intended for administration once daily. Thus, a major disadvantage of the once-a-day treatment in the art may be a low plasma concentration at the end of the dosing period and thereby the lack of therapeutic response. As the treatment of pain and/or inflammatory conditions and/or related conditions, is a balance of therapeutic effect on the one hand and the risk of side effects on the other hand, e.g. due to accumulation of drug, the dosage interval is generally calculated so that the drug concentration is substantially decreased at the time of intake of the next dosage. Accordingly, the patient will very often suffer from disease symptoms before the drug concentration subsequent to the next dosage has reached the therapeutic level. In addition, it should be noted that in the treatment of pain and/or inflammatory conditions and/or related conditions, relatively higher dosages, corresponding to a relatively higher peak concentration, are often needed in case the symptoms break through. Accordingly, a relatively higher initial plasma concentration of an NSAID substance may be necessary compared to the plasma concentration at steady state.

[0012] However, to the best of our knowledge no oral non-steroid anti-inflammatory modified release pharmaceutical composition has been disclosed which at the same time can be produced in an easy, cheap and reliable manner and which provides a suitable profile for release of active substance (under acidic, neutral and basic conditions) resulting in an extended period of action so that the inflammatory condition is both rapidly alleviated after administration and

avoided for a period of about 12 to 24 hours.

[0013] Therefore, there is a need for developing a composition comprising a non-steroid anti-inflammatory drug substance permitting the administration of dosages only once or twice a day in a safe and reliable manner, and which is easy to produce, preferably involving conventional production methods and as few production steps as possible. It is also important that an NSAID composition for daily administration comprises the active ingredient in such a way that the composition has a reliable dissolution rate since a change in the dissolution pattern of the NSAID substance could be disadvantageous for the patient.

BRIEF DISCLOSURE OF THE INVENTION

[0014] The purpose of the present invention is to provide an oral modified release multiple-units composition for administration of a daily dosage of an NSAID substance in a dosage form which only requires administration at the most twice daily, preferably once daily, and which overcomes the drawbacks of hitherto suggested formulations of modified release compositions containing an NSAID substance in that the dosage form both provides a substantially fast release from a first fraction comprising multiple units and a delayed and extended release from a second fraction of multiple units of the NSAID substance whereby alleviation of symptoms is achieved shortly after administration and is maintained for at least 12 hours, preferably 24 hours after administration.

[0015] A further aspect of the invention is to provide a process for the preparation of a composition of an oral pharmaceutical modified release multiple-units composition containing an NSAID substance, and in addition, a method for treating patients with a composition according to the invention whereby the interval between each administration is increased to about 12-24 hours.

[0016] Accordingly, the present invention relates to an oral pharmaceutical modified release multiple-units composition in unit dosage form for administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance (an NSAID substance), a unit dosage form comprising two NSAID-containing fractions,

i) a first NSAID-containing fraction of multiple-units for quick release of the NSAID substance, and

ii) a second NSAID-containing fraction of multiple-units for extended release of the NSAID substance,

the first fraction which - when subjected to dissolution method II as defined herein employing 0.07 N HCl as dissolution medium - releases at least 50% w/w of the NSAID substance present in the fraction within the first 20 min of the test, the second fraction being in the form of coated delayed release multiple-units for extended release of the NSAID substance.

[0017] The present invention also relates to a composition for the administration of a therapeutically and/or prophylactically effective amount of an NSAID substance to obtain both a relatively fast onset of the therapeutic effect and the maintenance of a therapeutically active plasma concentration for a relatively long period of time, a unit dosage of the composition comprising at least two fractions as follows:

a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically and/or prophylactically active plasma concentration within a relatively short period of time, and

a second fraction of coated modified release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically and/or prophylactically active plasma concentration in order to enable dosing once or twice daily,

the formulation of the first and the second fractions, with respect to release therefrom and with respect to the ratio between the first and the second fraction in the unit dosage, being adapted so as to obtain:

a relative fast *in vitro* release of the NSAID substance from the first fraction of quick release multiple-units, as measured by the dissolution method II as defined herein,

an extended *in vitro* release of the NSAID substance from the second fraction of extended release multiple-units relative to the *in vitro* release of the first fraction of the NSAID substance, as measured by the dissolution method III as defined herein,

the quick release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 50% w/w release of

the NSAID substance contained in the

first fraction at the time when at the most about 15% w/w such as, e.g., at the most about 10% w/w or at the most about 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III as defined herein.

[0018] It should be noted that the dissolution methods mentioned above and throughout the specification of course may be adjusted to specific drug substances and in some cases replaced with other dissolution methods. However, the requirements claimed herein should still be fulfilled.

[0019] The modified release multiple-units dosage forms of the present invention achieve and maintain therapeutic plasma concentrations for a prolonged period of time. In order to achieve the relatively fast absorption for the first fraction it requires that NSAID substances dissolve in the stomach (cf. the discussion above). Since the solubility of an NSAID substance such as, e.g., lornoxicam is < 1 mg /100 ml in 0.1 N HCl (aqueous solution of 0.1 N hydrochloric acid) the present inventors have found that incorporation such an NSAID substance in free form or in the form of a traditional formulation does not give the desired quick release under acidic conditions to enable a fast onset of the therapeutic effect *in vivo*. However, and as it will be discussed in detail below, a quick release of an NSAID substance (which is a weak acid or has a very low solubility under acidic conditions) takes place under acidic conditions provided that the drug substance is presented in a formulation wherein specific means has been used in order to manipulate the release rate so that the release becomes much faster than from a traditional composition. Thus, in contrast to the prior art composition in which focus only has been on the extended release rate part of the compositions and on the possibility of changing the release from this part, the present inventors have found it necessary to adjust the release rate from both the fast and the slow release part of a composition when the NSAID substance either has a very low solubility in 0.1 N hydrochloric acid or has a pK_a below about 5.5 such as, e.g., about 4-5. Thus, both the fast release fraction and the delayed release fraction must be manipulated with respect to release in order to achieve a suitable overall release rate.

[0020] The first fraction of the composition constitutes the quick releasing part of the composition whereas the second fraction of the composition constitutes the delayed and extended release part of the composition. In the first fraction, the release rate is primarily governed by the formulation of the fraction, i.e. the ingredients employed and the processing of the ingredients to obtain the first fraction (cf. Danish Patent Application filed on 10 September 1998 in the name of Nycomed Danmark). In those cases, where a coating is present on the units of the first fraction, the coating may of course also contribute to the control of the release of the active drug substance from the first fraction. In the second fraction, the release rate is primarily governed by the constitution and thickness of a controlled release membrane which are applied on pellet cores (also denoted "pellets").

[0021] The delayed and extended fraction is based on the application of a release controlling membrane. The release is being controlled by the membrane which makes the formulation much more robust and easier to manipulate and manufacture. Ideally there is no release controlling effect from the uncoated units of the second fraction, i.e. the uncoated multiple-units of the second fraction do not significantly contribute to any control of the extended release of the active drug substance but the uncoated multiple-units merely release the active drug substance freely without any significant retardation.

[0022] The modified release multiple-units dosage forms of the present invention achieve and maintain therapeutic levels and, at the same time, reduces the risks for any side effect, which are believed to be associated with high blood levels of NSAID substances. Furthermore, the delayed or extended release properties of the coating applied on the second fraction of the multiple-units dosage forms of the present invention are unaffected by the pH in the gastro-intestinal tract.

[0023] The first fraction of the multiple-units dosage form of the invention may also be in the form of coated multiple-units provided that the release rate of such a fraction is so fast in the dissolution medium employed in dissolution method II described herein that at least 50% w/w of the total dose of the first fraction is released within the first 20 min.

[0024] When a coating is present on the multiple-units of the first fraction then it could advantageous be of the same kind as an outer coating on the multiple-units of the second fraction. The employment of the same kind of coating for each fraction may be performed with substantially identical procedures and materials and the production cost can be kept at a low level.

DETAILED DISCLOSURE OF THE INVENTION

[0025] Accordingly, the present invention relates to an oral pharmaceutical modified release multiple-units composition in unit dosage form for administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance (an NSAID substance), a unit dosage form comprising two NSAID-containing fractions,

i) a first NSAID-containing fraction of multiple-units for quick release of the NSAID substance, wherein said fraction comprises an and acid substance or an alkaline agent, and

ii) a second NSAID-containing fraction of multiple-units for extended release of the NSAID substance,

the first fraction which - when subjected to dissolution method II as defined herein employing 0.07 N HCl as dissolution medium - releases at least 50% w/w of the NSAID substance present in the fraction within the first 20 min of the test, the second fraction being in the form of coated delayed release multiple units, said units coated with a coating that is water-insoluble, but water-diffusible and pH-independent.

[0026] As discussed above it is very important to secure that the release pattern of the active drug substance contained in the composition is suitable for a composition for administration once or twice daily. The employment of at least two different fractions of multiple-units gives very flexible formulation parameters. Thus, it is possible to vary i) the percentage of the total dose of the NSAID substance contained in each fraction and ii) the weight ratio between the different fractions. The system (i.e. formulation concept) is therefore very suitable to not only one specific drug substance but can within certain limits be applied on a class or many classes of active drug substances once the target release profile has been determined. Of course, a change from one active drug substance to another active drug substance may give rise to certain adjustments of the constitution of the individual fractions to the specific substance. In the following is given a discussion of how to determine a target profile for an active drug substance and the release requirements generally applicable for the group of active drug substances belonging to the non-steroid anti-inflammatory drug substances.

Dissolution requirements

[0027] As described in the following, a target release profile can be designed for any NSAID substance. In the following the target release profile for a selected NSAID substance is described, namely lornoxicam.

[0028] Based on the knowledge of the pharmacokinetics of lornoxicam and a study performed by us employing a plain tablet and a solution (Hitzenberger G, Radhofer-Welte S, Takacs F, Rosenow D.: Pharmacokinetics of lornoxicam in man, Postgrad. Med. J. 1990, 66, pp S22-S26), a target in vivo profile for a once daily product has been estimated (Figure 1).

[0029] The presumptions made in estimating this target profile were:

i) a double peak and an effective concentration for 24 hours are desired from a therapeutic point of view (i.e. plasma lornoxicam concentrations at 24 hours should be similar to the plasma concentration obtained 8-12 hours after administration of half the dose in the form of a plain tablet),

ii) that the first fraction of the composition should have an absorption rate similar to or faster than that of plain tablets

iii) that the peak concentration should not be higher than the peak concentration observed after administration of half the dose in the form of a plain tablet, and

iv) that the second peak should appear about 5-6 hours after dosing.

[0030] A person skilled in the art is capable of determining the actual values with respect to the above-mentioned provisions and based on such values perform any necessary correction to the estimated profile (target profile).

[0031] The estimated target plasma profile as well as the profile from plain tablets have been deconvoluted with plasma concentrations from an oral solution to give an estimated *in vivo* dissolution profile (Figure 2). All data were normalised to a dose of 16 mg. In the deconvolution a time interval of 0.5 hours was employed (cf. Langenbucher F., and H.

[0032] Möller: Correlation of *in vitro* drug release with in vivo response kinetics. Part I:

Mathematical treatment of time functions. Pharm. Ind. 1983, 45, pp 623-8 and
Langenbucher F. and H. Möller: Correlation of in vitro drug release with in vivo response kinetics. Part II: Use of function parameters. Pharm. Ind. 1983, 45, pp 629-33).

[0033] The presumptions in making this deconvolution were that the daily dose of lornoxicam is the same irrespective of whether a once daily composition or a plain tablet or a solution were administered,

[0034] The estimated *in vivo* dissolution profile for a once daily product can be used as the target *in vitro* profile for the combination of a fast or quick release fraction (i.e. the first fraction) and an extended or slow release fraction (i.e.

the second fraction, coated pellets). The estimated *in vivo* dissolution profile for the once daily composition can be used as the target *in vitro* profile, when performing the dissolution tests *in vitro* with 1 hour in 0.1 N HCl and then shift to phosphate buffer pH 7.3 or 7.4 (dissolution methods III or IV described herein). This knowledge has been utilized in order to arrive at the dissolution requirements described in the following.

[0035] The presumptions made in using the estimated *in vivo* profile as target for *in vitro* profile were:

i) that a plain tablet will remain in the stomach for about 1 hour before a passage into the intestine takes place (estimated from the difference in T_{max} between the solution (0.5 hours) and the plain tablet (1.5 hour),

ii) that the correlation between the *in vitro* dissolution and the *in vivo* dissolution is a 1:1 correlation, and

iii) that lornoxicam is absorbed through the whole gastrointestinal tract (including colon) in order not to loose any amount of active drug substance ready for absorption into the circulatory system.

[0036] Before going into detail with respect to the release requirement to the first fraction, the second fraction and the composition in its final form, in the following is given details with respect to the target release profile for a once daily lornoxicam composition. The target profile has been estimated as described above.

[0037] Target release *in vivo* profile (corresponds to target release profile *in vitro* employing dissolution methods III or IV as described herein):

Time (hours)	% w/w released lornoxicam
0.5	21 (range: 10-25%)
1	29 (range: 15-35%)
2	37 (range: 25-45%)
3	42 (range: 30-55%)
4	52 (range: 40-65%)
5	62 (range: 45-70%)
6	69 (range: 50-75%)
7	75 (range: 55-80%)
8	79 (range: 60-85%)
9	83 (range: 60-90%)
10	86 (range: 60-95%)
12	89 (range: 65-99%)
16	94 (range: at least about 85%)
20	97 (range: at least about 90%)
24	100 (range: at least about 90%)

[0038] As apparent from the above, the first fraction must release the active drug substance very quickly in 0.1 N HCl or in the dissolution medium employed in dissolution method II described herein, i.e. under conditions simulating the conditions in the stomach and under these conditions the second fraction does not release any significant amount of the active drug substance. In this connection it is important to note that even if the second fractions does not release any significant amount of the active substance within the first 20 min or 1 hours under acidic conditions, then the controlled release coating is not necessarily designed as an enteric coating, i.e. a coating which is insoluble at acidic pH and soluble at neutral/basic pH. The compositions according to the invention exemplified in the experimental section are examples on compositions wherein the controlled release coating of the second fractions is not an enteric coating. Furthermore, application of an enteric coating on e.g. pellets would not lead to an extended release of an active drug substance. The release will of course be delayed (no release under acidic conditions) but as the pH becomes neutral and alkaline, then the enteric coating dissolves, i.e. there is no membrane left to control the release.

[0039] Notably, the release of the active drug substance from the first fraction is at least 55% w/w such as, e.g., at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w or at least about 80% w/w of the total NSAID substance present in the first fraction within the first 20 min of the test, i.e. the dissolution method II (pH corresponding to 0.07 N HCl) as defined in the experimental section.

[0040] In one embodiment the composition may comprise modified release multiple units wherein the *in vitro* dissolution characteristics of the first fraction of quick release multiple-units within 0.5 hour provides a release as defined by the dissolution methods II as described herein of at least about 50% w/w, at least about 60% w/w, at least about

70% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w calculated on the total amount of active drug substance contained in the first fraction.

[0041] In addition, the composition may comprise modified release multiple units wherein the *in vitro* dissolution characteristics of the first fraction of quick release multiple units within 1 hour provides a release as defined by the dissolution methods II described herein of at least about 50% w/w, such as, e.g., at least about 60% w/w, at least about 70% w/w, at least about 80% w/w, at least about 85%, at least about 90% w/w or at least about 95% w/w calculated on the total amount of active drug substance in the first fraction.

[0042] As apparent from the discussion above, the overall release characteristics with respect to release of the active drug substance from the final composition are composed of the release characteristics of the first and the second fraction of multiple-units, respectively. With regard to compositions containing an NSAID substance intended for administration once or twice daily, the present inventors have found that the release characteristics of the second fractions most suitably should have the following order of magnitude provided that the release characteristics of the first fraction are as discussed above.

[0043] Accordingly, the *in vitro* dissolution characteristics of the second fraction of extended release multiple units may in one embodiment within 1 hour provide a release as defined by the dissolution method III described herein in the range of 0%- about 30% w/w, such as, e.g., in the range of 0%- about 20% w/w, in the range of 0%-about 10%w/w such as about 5% w/w calculated on the total amount of active drug substance in the second fraction.

[0044] Furthermore, the *in vitro* dissolution characteristics of the second fraction of extended release multiple units may within 3 hours provide a release as defined by the dissolution method III described herein in the range of about 10%-70% w/w, such as, e.g., in the range of about 10%-60% w/w, in the range of about 12%-50% w/w, in the range of 14%-45% w/w, in the range of about 15%-30% w/w, in the range of about 15%-20% w/w such as, e.g., about 17% w/w of the NSAID substance.

[0045] Within 6 hours, the *in vitro* dissolution characteristics of the second fraction of extended release multiple units may provide a release as defined by the dissolution method III described herein in the range of about 35%-95% w/w, such as, e.g., in the range of about 50%-90% w/w, in the range of about 50%-80% w/w, in the range of 50%-75% w/w, in the range of about 50%-60% w/w, in the range of about 53%-59% w/w such as, e.g. about 56% w/w of the NSAID substance.

[0046] In addition, within 9 hours the *in vitro* dissolution characteristics of the second fraction of extended release multiple units may provide a release as defined by the dissolution method III described herein in the range of about 50%-100% w/w, such as, e.g., in the range of about 60%-98% w/w, in the range of about 65%-95% w/w, in the range of about 70%-90% w/w, in the range of about 70%-80% w/w such as, e.g., about 76% w/w of the NSAID substance.

[0047] To ensure that the final composition has a proper constitution with respect to the weight amount of first fraction relative to the amount of second fraction, the *in vitro* dissolution characteristics of the first and second fractions are in one embodiment adapted so that the first fraction is substantially released when the release from the second fraction is initiated, corresponding to at least 50% w/w release of the first fraction at the time at the most about 15% w/w such as, e.g., at the most about 10% or at the most about 5% w/w of the second fraction is released, as measured by the dissolution method III described herein. In addition, the *in vitro* dissolution characteristics of the first and second fractions in the same or a second embodiment as mentioned above are adapted so that the first fraction is substantially released when the release from the second fraction is initiated, corresponding to at least 70% w/w release of the first fraction at the time at the most about 20% w/w such as, e.g., at the most 15% w/w or at the most about 10% w/w of the second fraction is released, as measured by the dissolution method III described herein.

[0048] Apart from the requirements to the individual fractions contained in the composition it is of course of utmost importance to ensure that the composition in its final form has *in vitro* dissolution characteristics which give evidence for a suitable *in vivo* behaviour, i.e. a fast onset of the effect together with an extended release of the active drug substance to ensure a therapeutic and/or prophylactic effect upon administration once or twice daily.

[0049] The two fractions of multiple units may be selected, with respect to the release from each fraction and the ratio between the two fractions, so that the *in vitro* dissolution characteristics of the composition within 1 hour provide a release of the NSAID substance in the first and second fractions in the range of from about 5% w/w to about 50% w/w, such as, e.g., in the range of from about 5% w/w to about 45% w/w, in the range of from about 15% w/w to about 40% w/w, in the range of from about 20% w/w to about 35% w/w such as about 29% w/w, as defined by the dissolution method III described herein.

[0050] In addition, the two fractions of multiple units may be selected, with respect to the release from each fraction and the ratio between the two fractions, so that the *in vitro* dissolution characteristics of the composition within 3 hours provide a release as defined by the dissolution method III described herein in the range of from about 20% w/w to about 80% w/w, such as, e.g., in the range of from about 25% w/w to about 70% w/w, the range of from about 30% w/w to about 60% w/w, in the range of from 35% w/w to about 55% w/w such as about 42% w/w.

[0051] In an additional aspect, the two fractions of multiple units may be selected, with respect to the release from each fraction and the ratio between the two fractions, so that the *in vitro* dissolution characteristics of the composition

within 6 hours provide a release as defined by the dissolution method III described herein in the range of from about 40% w/w to about 98% w/w, such as, e.g., in the range of from about 50% w/w to about 95% w/w, in the range of from about 60% w/w to about 90% w/w, in the range of from about 60% w/w to about 85% w/w, in the range of from about 60% to about 83% such as about 69-70% w/w.

[0052] Furthermore, the two fractions of multiple units may be selected, with respect to the release from each fraction and the ratio between the two fractions, so that the *in vitro* dissolution characteristics of the composition within 9 hours provide a release as defined by the dissolution method III described herein in the range of from about 50% w/w to about 100% w/w, such as, e.g., in the range of from about 60% w/w to about 99% w/w, in the range of from about 70% w/w to about 98% w/w, in the range of from about 70% w/w to about 97% w/w, in the range of from about 75% w/w to about 96% w/w, such as in the range of from about 80% w/w to about 96%, such as about 80-85% w/w.

[0053] In a preferred embodiment, the composition fulfils the above criteria with respect to the dissolution characteristics of the composition in the full time span mentioned.

[0054] The percentage of NSAID substance in the first fraction is in the range of about 5%-50% w/w such as, e.g., in the range of about 10%-45% w/w, in the range of about 15%-45% w/w, in the range of about 20%-40% w/w, in the range of about 25%-40% w/w, in the range of about 25%-35% w/w such as, e.g., about 30% w/w, calculated on the total amount of NSAID substance in the composition.

[0055] The percentage of NSAID substance in the second fraction is in the range of about 30%-99% w/w such as, e.g. in the range of about 40%-98% w/w, in the range of about 45%-95% w/w, in the range of about 50%-95% w/w, in the range of about 55%-85% w/w, in the range of about 60%-80% w/w, in the range of about 60%-75% w/w, in the range of abut 65%-75% w/w such as, e.g., about 70% w/w, calculated on the total amount of NSAID substance in the composition.

[0056] In a preferred embodiment, the multiple units of the second and, when appropriate, the first fraction are coated, cross-sectionally substantially homogeneous pellets. It is preferred that the multiple units of the first fraction result in a peak plasma concentration of the NSAID substance which is substantially the same as the peak concentration resulting from the second fraction. As the peak plasma concentration of the second fraction is adapted so that plasma concentration has a prolonged character due to the dissolution characteristics of the fraction described herein, the peak of this second fraction should preferably substantially represent the upper level of the therapeutic plasma concentration. In a preferred embodiment, the plasma concentration level is of such a size that no NSAID substance is in excess.

[0057] Since the total amount of NSAID substance contained in the first fraction is balanced compared to the total amount of NSAID substance in the composition, a peak plasma concentration of NSAID substance derived from the first fraction which is higher than the peak concentration resulting from the second fraction does not necessarily represent a substantial waste of the NSAID substance.

[0058] However, unless the patient suffers from heavy breakthrough symptoms wherein a higher plasma concentration than the plasma concentration for maintaining symptom alleviation often seems to be needed, the concentrations obtained from the first fraction should not exceed the peak from the second fraction.

[0059] Even in the circumstances wherein the peak of the first fraction is preferably higher than the peak from the second fraction, unsuitable high plasma concentrations (within the toxic level) derived from the first fraction may easily be avoided by adjusting the amount of active drug substance contained in the first fraction.

[0060] In another embodiment, e.g. in the circumstances wherein the patient is well treated by administration once or twice a day with a composition according to the invention, the first fraction may be adapted so that it results in a peak plasma concentration of the NSAID substance which is lower than the peak concentration resulting from the second fraction. This would not necessarily result in breakthrough symptoms as the NSAID substance remaining in the plasma from the previous dosage administered may contribute to maintaining the plasma concentration sufficiently high until the second fraction of the composition is released. In other cases, the daily dosage may be administered at a suitable time of the day when the patient has experienced less need for the NSAID, e.g. before bedtime.

[0061] Accordingly, an important aspect of the invention is an embodiment wherein the first fraction results in a therapeutically active plasma concentration of the NSAID substance until the delayed release of an NSAID substance from the second fraction of modified release multiple units contributes to the maintenance of a therapeutically active plasma concentration of the NSAID substance.

[0062] As discussed above, the multiple-units of the first fraction may be in the form of uncoated pellet cores, coated pellet cores, granules, a granulate or small plain tablets provided that the requirements with respect to release of active drug substance in 0.1 N HCl and under conditions as those described under dissolution method II herein are fulfilled. In those cases, where the first fraction is in the form of coated pellets, the time lag of the release from the second fraction relative to the first fraction may be obtained by a modified release coating of the second fraction which is present in a range of about 2%-80% such as, e.g., about 2%-70%, about 2-60%, about 3-50%, about 3-40%, about 4-30%, about 5-20% or about 2-5%, relative to the uncoated unit.

[0063] It is also preferred that the modified release coating of the fraction(s) is substantially water-insoluble, but

water-diffusible and substantially pH-independent which will facilitate an absorption independent of the presence of food in the stomach.

Dosage

[0064] In general, the dosage of the active drug substance present in a composition according to the invention depends *inter alia* on the specific drug substance, the age and condition of the patient and of the disease to be treated.

[0065] Compositions according to the invention intended for once daily administration will generally contain a daily dose of the active drug substance whereas compositions according to the invention intended for twice daily administrations will generally contain half the daily dose of the active drug substance. However, the daily dose may be divided into several dosage forms.

[0066] In the following is listed the recommended daily doses for selected NSAID substances.

Aceclofenac: 200 mg
Diclofenac: 100 mg
Etodolac: 400 mg
Fenbufen: 900 mg
Fenoprofen: 1.5 g
Flurbiprofen: 200 mg
Ibuprofen: 1.6 g
Indometacin: 100 mg
Ketoprofen: 200 mg
Meloxicam: 15 mg
Nabumeton: 1 g
Naproxen: 750 mg
Piroxicam: 20 mg
Sulindac: 300 mg
Tenoxicam: 20 mg
Tiaprofenic acid: 600 mg
Tolfenamic acid: 400 mg
Tolmetin: 800 mg

[0067] The amount of an NSAID substance of the modified release multiple-units composition according to the invention may be selected so that is corresponds to about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 8 mg, 10 mg, 12 mg, 16 mg, 20 mg, 24 mg, 25 mg, 30 mg, 32 mg, 50 mg, 60 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1 g, 1.1 g, 1.2 g, 1.3 g or 1.6 g of NSAID substance which are dosages generally known in the art. However, the composition according to the invention preferably comprises an amount of an NSAID substance which is a daily therapeutically effective amount of the NSAID substance.

[0068] Generally, with conventional dosage forms such as plain tablets comprising an NSAID substance, it is not always possible to obtain identical release profiles when different dosages are administered together as the load of active ingredient may differ depending on the size of the tablet. The release profile for 100 mg given in a single dosage may thus differ from 100 mg given as 5 dosages comprising 20 mg each. Not even with the commercially available modified release dosage forms, a substantially identical release profile within the different dosages is always observed.

[0069] With a composition according to the present invention, it is now possible to administer different dosages with identical release profiles (cf. results reported in the experimental section). For example, if each modified release multiple-units composition according to the invention is prepared with the same type of multiple units of the first and second fractions and in the same ratios, each of the dosage forms may be administered together to obtain any desired total dosage without altering the overall release profile from the total dosage. Accordingly, reliable and predictable plasma concentrations during the complete time span between administration may be obtained independently of the total dosage.

[0070] Therefore, a further advantage of the composition according to the invention is that the composition may be produced in different series of dosage forms of e.g. 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, 32 mg etc., each of the series having individual properties resulting from the design of modified release of the first and second fractions as well as from the ratio between the fractions. Any desired total dosage can then be selected from the relevant dosage forms within each of the series.

[0071] The preferred dosage form according to the invention is in the form of a capsule, tablet, sachet etc. The size of the dosage form is adapted to the amount of the NSAID substance of the composition.

[0072] The above suggested dosage amounts should not be regarded as a limitation of the scope of the invention

as it is obvious for the skilled person that any desired amount of the NSAID substance may be applied and is only limited by the size of the composition and the type of the NSAID substance.

[0073] The overall goal of the present invention is to provide a composition in unit dosage form for the administration of a therapeutically effective amount of an NSAID substance once a day. However, as some patients may still need to, or prefer to, receive administration twice a day, the invention should not be limited to a once-a-day composition as long as each of the unit dosage forms fulfils the criteria with respect to the dissolution mentioned above.

[0074] In a further aspect, the invention relates to a process for the preparation of an oral pharmaceutical modified release composition, the process comprising incorporating into the unit dosage at least two fractions as follows:

a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically or prophylactically active plasma concentration within a relatively short period of time, and a second fraction of coated extended release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically active plasma concentration in order to enable dosing once or twice daily,

the formulation of the first and the second fractions, with respect to release therefrom and with respect to the ratio between the first and the second fraction in the unit dosage, being adapted so as to obtain:

a relative quick *in vitro* release of the NSAID substance from the first fraction of quick release multiple-units, as measured by the dissolution method II defined herein,

an extended *in vitro* release of the NSAID substance from the second fraction of extended release multiple-units relative to the *in vitro* release of the first fraction of the NSAID substance, as measured by the dissolution method III as defined herein, the quick release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least about 50% w/w release of the NSAID substance contained in the first fraction at the time when about 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III as defined herein.

Definitions of selected terms used herein

[0075] The term "modified release multiple-units composition" used in the present context is defined as the release of the drug differs from that of a traditional composition. The release rate is in other words controlled and it is possible to manipulate the release rate by means of e.g. changing the formulation parameters. The rate is often controlled in such a manner that the plasma concentration levels are maintained for the longest possible period above the therapeutic (the therapeutically active) level, but below the toxic level. However, the term "modified" is not restricted to an extended or prolonged effect, the term "modified" may as well cover the situation where the release rate is manipulated in such a manner that a quicker release than normally expected is obtained. Thus, in the present context the terms "quick" , "fast" and "enhanced" release as well as "controlled", "delayed", "sustained", prolonged", "extended" and other synonyms well known to a person skilled in the art are covered by the term "modified".

[0076] The term modified release in the present context refers to a composition which can be coated or uncoated and prepared by using pharmaceutically acceptable excipients and/or specific procedures which separately or together are designed to modify the rate or the place at which the active ingredient or ingredients are released (Ph. Eur. **97**).

[0077] The term "extended release" in the present context refers to a modified release composition of which the release of the active ingredient and its subsequent absorption are prolonged in comparison with a conventional non-modified form (Commision of the European Communities).

[0078] The terms "quick release", "fast release" or "enhanced release" in the present context refer to a modified release composition of which the release of the active ingredient and its subsequent absorption are fast. More specifically, the terms "quick release", "fast release" or "enhanced release" mean that for a composition - when subjected to a dissolution method II described herein - at least about 50% w/w of the active substance is dissolved within the first 20 min of the test.

[0079] The term "fraction" of multiple units in the present context refers to a part of the multiple units of a dosage unit. One fraction will generally differ from another fraction of multiple units of the dosage unit. Even though only two fractions have been defined, it is within the scope of the invention to have more than two fractions in one dosage unit. Accordingly, the dosage unit according to the invention comprises at least two fractions.

[0080] The term "dosage unit" in the present context refers to one single unit, e.g. a capsule, tablet, a sachet or any other relevant dosage form known within the art. A dosage unit represents a plurality of individual units which in accordance with the general state of the art may be in the form of a capsule, a tablet, a sachet, etc.

[0081] The term "bioavailability" designates the rate and extent to which the drug is absorbed from the modified

multiple-units composition.

[0082] In the present context the term "therapeutically active plasma concentration which enables dosing once or twice daily" includes the situation wherein the NSAID substance administered has been metabolised to active metabolites resulting in a therapeutic effect for the stated period. It also includes the situation wherein the NSAID substance administered is present in a periferal compartment resulting in a therapeutic effect for the stated period.

[0083] The terms "NSAIDs" or "NSAID substances" are used herein to designate a group of drugs that belongs to non-steroid anti-inflammatory drug substances and pharmaceutically acceptable salts, prodrugs and/or complexes thereof as well as mixtures thereof.

[0084] The therapeutic classes mentioned herein are in accordance with the ATC (Anatomical Therapeutic Chemical) classification system.

Active drug substances

[0085] In the following are given examples of active drug substances which may be incorporated in a composition according to the invention. A majority of the active drug substances mentioned are weak acids, i.e. substances which have a pK_a value below about 5.5 such as, e.g., in a range of from about 3.0 to about 5.5 or in a range of from about 4.0 to about 5.0. In this connection it can be mentioned that the pK_a value for lornoxicam is about 4.7, for naproxen about 4.2, for indometacin about 4.5 and for acetylsalicylic acid about 3.5. When such substances which have a pK_a value of between about 3.0 to about 5.5 is employed in the composition, the present inventors have found that the first fraction should be in the form of uncoated multiple-units as the coating or the manufacture of the units to a form suitable for application of a coating seem to have a retarding effect on the release rate of the active drug substance from the first fraction (see the experimental section). Moreover, active drug substances like those mentioned above (i.e. weak acids having a pK_a value of at the most about 5.5 or about 5.0) generally have a poor solubility in media having a pH below the pK_a value; as an example the solubility of lornoxicam at a pH corresponding to 0.1 N HCl is less than about 1 mg/100 ml at room temperature and active drug substances like acetylsalicylic acid, indometacin and naproxen are regarded as substances which are practically insoluble in water and 0.1 N HCl at room temperature. From the discussion relating to solubility and availability of the active drug substance in order to get access to the circulatory system it is should be appreciated that the release (dissolution) of the active drug substance from the first fraction should be quick under acidic conditions, e.g., in 0.1 N HCl even if the active drug substance has a very low solubility in this medium. First fractions containing such active drug substances are generally not in the form of coated multiple-units in compositions according to the invention (cf. the discussion above).

[0086] However, when the active drug substance incorporated in a composition according to the invention has a pK_a value of at least about 5.0 such as at least about 5.5 the multiple-units of the invention may as well be in the form of coated multiple-units such as, e.g., coated pellet cores.

[0087] The first fraction is normally uncoated when the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at the most about 0.5% w/v such as, e.g. at the most about 0.1% w/v, at the most about 0.05% w/v, at the most about 0.03% w/v, at the most about 0.01 % w/w, at the most about 0.007% w/v, at the most about 0.005% w/v, at the most about 0.003% w/v, at the most about 0.002% w/v or at the most about 0.001% w/v.

[0088] The first fraction may be coated when the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at least about 0.1 % w/v such as e.g. at least about 0.5% w/v or at least about 1 % w/v.

[0089] Relevant examples of NSAID substances suitable for use in compositions according to the invention are:

- aminoarylcarboxylic acid derivatives like e. g. enfenamic acid, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, morniflumate, niflumic acid, and tolfenamic acid,
- arylacetic acid derivatives like e.g. aceclofenac, acemetacin, amfenac, bromfenac, cimmetacin, diclofenac, etodolac, fentiazac, glucametacin, indomethacin, lonazolac, metiavinic acid, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, and zomepirac,
- arylcarboxylic acids like e.g. ketorolac and tinoridine,
- arylpropionic acid derivatives like e. g. alminoprofen, bermoprofen, carprofen, dexibuprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, ketoprofen, loxoprofen, naproxen, oxaprozin, pranoprofen, protizinic acid, and tiaprofenic acid,
- pyrazoles like e.g. epirizole,
- pyrazolones like e.g. benzpiperylon, mofebutazone, oxyphenbutazone, phenylbutazone, and ramifenazone,
- salicylic acid derivatives like e.g. acetaminosalol, acetylsalicylic acid, benorylate, eterisalate, fendosal, imidazole salicylate, lysine acetylsalicylate, morpholine salicylate, parsalmide, salamidacetic acid and salsalate,
- thiazinecarboxamides like a.o. ampiroxicam, droxicam, lornoxicam, meloxicam, piroxicam, and tenoxicam,
- others like bucillamine, bucolome, bumadizon, diferenpiramide, ditazol, emorfazone, nabumetone, nimesulide, proquazone and piroxicam (e.g. in the form of a betacyclodextrin complex).

[0090] From a market point especially the following NSAIDs are interesting: lornoxicam, diclofenac, nimesulide, ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen, ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acemetacin, morniflumate, meloxicam, flurbiprofen, tiaprofenic acid, proglumetacin, mefenamic, acid, fenbufen, etodolac, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen and pharmaceutically acceptable salts, complexes and/or prodrugs and mixtures thereof.

[0091] Other relevant active drug substances are COX-2 (COX is an abbreviation for cyclooxygenase) inhibitors like e.g. celecosib and flosulide.

[0092] At present, the most preferred drug substance is lornoxicam and pharmaceutically acceptable salts, complexes and prodrugs thereof. Lornoxicam may be present in a composition according to the invention as the sole drug substance or in combination with other drug substances.

[0093] The modified release oral dosage form of the present invention preferably includes an NSAID substance as the therapeutically active ingredient in an amount corresponding to from 1 to about 1600 mg of by weight. Alternatively, the dosage form may contain molar equivalent amounts of pharmaceutically acceptable salts thereof. The dosage form contains an appropriate amount to provide a substantially equivalent therapeutic effect.

[0094] A composition according to the invention may contain a further active drug substance. Relevant substances in this context are e.g. antidepressants, opioids, prostaglandine analogs (e.g. misoprostol), glucocorticosteroids, cytostatics (e.g. methotrexate), H_2 receptor antagonists (e.g. cimetidine, ranitidine), proton pump inhibitors (e.g. pantoprazole, omeprazole, lansoprazole), antacids, acetaminophen (paracetamol), penicillamine, sulfasalazine and/or auranorfin.

[0095] The term "antidepressant" used in the present context includes tricyclic antidepressants as well as other antidepressants and mixtures thereof. Pharmaceutically acceptable salts and/or complexes of antidepressant are also within the definition of antidepressant. Thus, the term "antidepressant" is used here to designate a group of drugs that have, to varying degrees, antidepressive properties and/or suitable properties with respect to alleviation or treatment of neurogenic pain and/or phantom pain. In the present context the term "antidepressant" encompasses drug substances mainly from the therapeutic class N06 or from the following drug classification: Psychoanaleptics excluding anti-obesity preparations; anti-depressants/thymoanaleptics including substances used in the treatment of endogenous and exogenous depression such as, e.g., imipramine, nortriptyline, amitriptyline, oxipramol and MAO-inhibiting substances; lithium; combinations of drugs with ataractics; psychostimulants including drugs which increase the psychic and physical performance and which have a fatigue depressing, stimulating effect such as, e.g., fentyllines, fencamfamine, methylphenidate, amphetamines; pyscholeptic-psychoanaleptic combinations; nootropics [which are a class of psychoactive drugs which are claimed to have a selective action on integrative functions of the CNS. Their action is alleged to be particularly associated with intellectual function, learning and memory. Nootropics include preparations containing substances such as piracetam, pyritinol, pyrisuccideanol maleate, meclofenoxate, cyprodenate and their combinations with other substances, excluding those products with a vasodilatory action (see the therapeutic class C04A). Combinations with cardiac glycosides are classified in the therapeutic class C01A.]; and neurotonics and other miscellaneous products including products which are not classified above such as single or combination products containing bisibutiamin, deanol and derivatives, GABA, GABOB, N-acetyl asparaginic acid glutaminic acid and salts, kavain, phospholipid, succinodinitrate.

[0096] The presently most interesting drug substances belong to the tricyclic antidepressants. Relevant examples of antidepressants are: tricyclic antidepressants such as, e.g. dibenzazepine derivatives like carpipramine, clomipramine, desipramine, imipramine, imipraminoxide, imipramine pamoate, lofepramine, metapramine, opipramol, quinupramine, trimipramine; dibenzocycloheptene derivatives like amitriptyline, amitriptyline and chlordiazepoxide, amitriptyline and medazepram, amitriptyline and pridinol, amitriptyline and perphenazine, amitriptylinoxide, butriptyline, cyclobenzaprine, demexiptiline, nortriptyline, nortriptyline and diazepam, nortriptyline and perphenazine, nortriptyline and fluphenazine, nortriptyline and flupentixol, noxiptilin, protriptyline; dibenzoxepine derivatives like doxepin; and other tricyclic anti-depressants like adinazolam, amoxapine, dibenzepin, dimetacrine, dosulepin, dosulepin and diazepam, dothiepin, fluacizine (fluoracyzine, toracizin), iprindole, maprotiline, melitracen, melitracene and flupentixol, pizotyline, propizepine, and tianeptine; other antidepressants like 5-hydroxytryptophan, ademetionine, amfebutamone, amfebutamone hydrochloride, amineptine, amineptine hydrochloride, amisulpride, fluoxetine hydrochloride, fluoxetine, hypericin, lithium carbonate, sertraline hydrochloride, sertraline, St John's wort dry extract, trimipramine maleate, citalopram, citalopram hydrobromide, clomipramine chloride, clomipramine hydrochloride, d-phenylalanine, demexiptiline, demexiptiline hydrochloride, dimethacrine tartrate, dothiepin, dothiepin hydrochloride, doxepin, fluphenazine hydrochloride, fluvoxamine, fluvoxamine hydrogen maleate, fluvoxamine maleate, ginkgo biloba, indalpine, isocarboxazide, johanniskrauttrockenestrakt, 1-tryptophan, lithium citrate, lithium sulfate, lofepramine, maprotiline, maprotiline hydrochloride, maprotiline mesilate, medifoxamine, metaprimine fumarate, mianserin, moclobemide, nitroxazepine hydrochloride, nomifensine, nomifensine maleate, nomifensin hydrogenmaleat, oxitriptan, paroxetine, paraoxetine hydrochloride, phenelzine, phenelzine sulfate, piracetam, pirlindole, pivagabine, prolintane hydrochloride, propizepine hydrochloride, protriptyline hydrochloride, quinupramine, remoxipride hydrochloride, rubidium chloride, setiptiline

maleate, tianeptine sodium, trazodone hydrochloride, venlafaxine hydrochloride, maprotiline, toloxatone, tranylcypromine, trazodone, trazodone hydrochloride, viloxazine, viloxazine hydrochloride,zimelidine, zimelidine dihydrochloride.

[0097] At present, the most interesting drug substances for use in a composition according to the invention are amitriptyline and/or imipramine and pharmaceutically acceptable salts, complexes and prodrugs thereof. Amitriptyline and/or imipramine may be present in a composition according to the present invention either as the sole drug substance or in combination with other drug substances. Amitriptyline is a very interesting drug candidate with respect to preventing and/or treating neurogenic pains and phantom pains.

[0098] The term "opioid" is used here to designate a group of drugs that are, to varying degrees, opium- or morphine-like in their properties. The term includes natural and synthetic opioids as well as active metabolites such as morphine-6-glucuronide and morphine-3-glucuronide, and mixtures of opioids. Pharmaceutically acceptable salts and/or complexes of opioids are also within the definition of opioids.

[0099] Further relevant examples of opioids for use in compositions according to the invention include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocondone, hydromorphone, hydroxypethidine, isomethadone, dextropropoxyphene, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, salts thereof, mixtures of any of the foregoing, mixed μ-agonists/antagonists, μ- and/or κ-agonists, combinations of the above, and the like.

[0100] Within the scope of the invention is of course that more than one active drug substance may be present in a composition, e.g. more than one NSAID substance and/or drug substances within the same or different therapeutic classes. Specific relevant therapeutic classes are M01A (NSAIDs), RO5D, N02 (analgesics), N2A (opioids) and N2B (non-narcotic analgesics).

Dose

[0101] In one embodiment of the present invention, the first fraction of multiple units comprises an amount of an NSAID substance corresponding to from about 50% to about 5% (between 1/2 and 1/20) of the daily dosage. In patients which are satisfactorily treated on 2-3 daily dosages of a conventional non-sustained formulation, the first fraction may in one example contain an amount of the NSAID substance corresponding to 40% of the daily dosage. The second fraction may then contain the remaining 60% of the daily dosage.

[0102] However, a preferred amount of the first fraction may comprise 30% of the daily dosage and the second fraction 70% of the daily dosage.

[0103] In another embodiment of the present invention, the first fraction of multiple units comprises an amount of an NSAID substance corresponding to the amount of the NSAID substance necessary for obtaining a therapeutic effect upon a first single oral dose of a conventional non-sustained formulation of the NSAID substance.

Formulation details

First fraction

[0104] As described above, the formulation of the first fraction depends on the specific active drug substance to be incorporated. If the solubility at room temperature in 0.1 N HCl is low and the pK_a value is below about 5.5. or 5.0, then the first fraction is in the form of uncoated multiple-units. A very suitable formulation of the first fraction has under such conditions been found to be in the form of a granulate wherein special means have been employed in order to ensure a quick release of the poor soluble active drug substance. The granulate is typically prepared by wet-granulation (a process well known for a person skilled in the art) employing as little organic solvent as possible in order to reduce any environmental and personal risk. Furthermore, the present inventors have found that incorporation of an antacid-like substance like, e.g., sodium bicarbonate (sodium hydrogencarbonate), magnesium carbonate, magnesium hydroxide, magnesium metasilicate aluminate and other alkaline substance, has a pronounced increasing effect on the release rate.

[0105] In one embodiment, the individual units of the relatively fast release fraction according to the invention will normally be a granulate having a size (average diameter) of at the most about 250 μm such as, e.g. at the most about 240 μm, at the most about 230 μm, at the most about 220 μm, at the most abut 210 μm, at the most about 200 μm, at

the most about 190 μm, at the most about 180 μm, at the most about 175 μm, at the most about 150 μm, at the most about 125 μm, at the most about 100 μm, at the most about 90 μm or at the most about 80 μm.

[0106] As described above, the first fraction may also be in the form of coated multiple-units such as coated pellets provided that the pK_a of the active drug substance is at least about 5.0 or 5.5. From the experimental section *inter alia* it appears that such coated cores may have the same coating as the coating of the second fraction, but the thickness of the coating differs in such a manner that the coating of the first fraction is much thinner than that of the second fraction. For further details with respect to coating see below.

Second fraction

[0107] The individual units of the extended release fraction according to the invention will normally be pellets or beads having a size (average diameter) of from about 0.1 to 2 mm. The most preferred pellet size is from 0.5 to 0.8 mm. The pellets or beads comprise a combination of active substance, the NSAID substance and excipients. When the pellets or beads are not coated, the combination of the active substance and the excipients is referred to as a core.

[0108] In the present context, the term "cores which are cross-sectionally substantially homogeneous" designates cores in which the active substance is not confined to an exterior layer on the core body, in other words normally cores which, through the cross-section of the core body, contain substantially the same type of composition comprising minor particles containing active substance, in contrast to the non-pareil type of cores which each consists of an excipient body with active substance applied to its surface. From this definition, it will be understood that the cores which are cross-sectionally substantially homogeneous will normally consist of a mixture of active substance with excipient(s), this mixture will not necessarily be qualitatively or quantitatively homogeneous through the total cross-sectional area of the core but may show, e.g., a concentration gradient of the NSAID substance or they may consist substantially solely of NSAID substance. In the following specification and claims, such cores which are cross-sectionally substantially homogeneous will, for the sake of brevity, often simply be designated "cores".

[0109] It is contemplated that the core comprising the NSAID substance in a substantially homogeneous form provides a more reproducible release of the active ingredient than compared to e.g. particles in which the active ingredient forms part of the coating.

[0110] It should, however, be understood that the invention is not limited to pellet formulation containing the above-mentioned cores; in principle, the type of cores can be any kind such as, e.g. matrices, non-pareil cores as well.

[0111] It is preferred that the release profile of the core of the individual unit is substantially non-limiting with respect to the desired release of the coated pellet, e.g. that the core itself provides at least about 90% w/w such as, e.g., at least about 95% w/w, at least about 97% w/w, at least about 98% such as about 100% release within 1 hour, measured in the *in vitro* dissolution test described in the Examples. However, pellet cores showing a slower release of the active substance are still within the scope of the invention.

Dosage forms

[0112] The oral pharmaceutical modified release multiple-units formulation according to the invention will typically be a capsule containing a multiplicity of the units, typically more than 100, a sachet containing a multiplicity of the units, typically more than 1000, or a tablet made from a multiplicity of the units, typically more than 100, in such a manner that the tablet will disintegrate substantially immediately upon ingestion in the stomach into a multiplicity of individual units which are distributed freely throughout the gastro-intestinal tract.

[0113] In the present context the term "once daily"/"once-a-day" is intended to mean that it is only necessary to administer the pharmaceutical formulation once a day in order to obtain a suitable therapeutic and/or prophylactic response; however, any administration may comprise co-administration of more than one dosage unit, such as, e.g., 2-4 dosage units if the amount of active substance required may not be formulated in only one composition unit or if a composition unit of a minor size is preferred.

[0114] In agreement with the above-mentioned definition of "once daily"/"once-a-day", "twice daily"/"twice-a-day" is supposed to mean that it is only necessary to administer the pharmaceutical formulation at the most twice a day in order to obtain a suitable therapeutic and/or prophylactic response in the patient.

[0115] Irrespective of the above-mentioned definitions of "once" and "twice" daily, a dosage unit constructed to deliver the active ingredient after only one daily administration is preferred. However, due to individual circumstances some patients may need a new dosage after e.g. 12 or 18 hours if the patient e.g. has an abnormal absorption or bowel transit time. If the individual has a relatively fast bowel transit time, some of the active ingredient may be excreted before the full dosage is released, or may be released in the colon from which the absorption may be decreased.

[0116] A multiple unit pharmaceutical composition according to the present invention is preferably formed as a unit dosage form which upon oral administration disintegrates into a multiplicity of individual units. The dosage unit form is preferably a solid dosage unit form such as, e.g., a tablet, a capsule, or a sachet, especially in the form of capsules.

[0117] The actual load of the NSAID substance in a pharmaceutical composition according to the invention, i.e. the concentration in % w/w of the NSAID substance calculated on the total weight of the multiple units, may depend on the particular NSAID substance employed in the formulation. The formulation principle employed in the present invention is very flexible. As an example it can be mentioned that compositions can be designed so that the load of the NSAID substance in the individual multiple units of the two fractions and the content of the two fractions for one dosage unit comprising e.g. 10 mg of NSAID substance is identical with another dosage unit comprising e.g. 100 mg, the release profile for each of the dosages will be identical. Consequently, an individual total dosage can be administered to the patient by combining the relevant dosage units e.g. selected from a series of 4, 8, 12, 16, 24 and 32 mg of the NSAID substance without altering the overall release profile of the total amount of the NSAID substance administered.

[0118] The compositions mentioned above may be prepared by conventional methods known in the art. The invention also relates to a method for preparing an oral pharmaceutical modified release multiple-units composition.

Coating

[0119] In a further embodiment, the invention relates to a method for preparing an oral pharmaceutical modified release multiple-units formulation in which

a) individual units containing an active substance are coated with an inner film-coating mixture ("the inner coat") comprising a film-forming substance,
b) the thus coated units are optionally provided with a first outer film layer comprising e.g. a stabilizing agent ("the middle coat"),
c) the thus coated units of the second fraction are optionally provided with a second outer film layer comprising a film-forming agent ("the outer coat"),
d) a mixture of individual units of the first and second fraction are formulated in a dosage form in the desired ratio of the two fractions.

[0120] In general, the inner coating is applied in an amount corrsponding to 2-20% w/w. The middle coating, if present, is applied in an amount corresponding to about 4% w/w of the uncoated units and the outer coat is applied in an amount corresponding to about 1-2% w/w of the uncoated units.

[0121] The film-forming agent of step c) may be so selected that adhesion between the units is prevented at elevated temperatures, the coated units are then subsequently heated to a temperature above 40 °C, preferably not above 65-75 °C, and thereby a continuous phase is formed in the inner film layer in homogeneous admixture with the film-forming substance. In some cases, this curing process may also take place before the outer coating layer may be applied.

[0122] The modified release coating is applied on the multiple units from a solution and/or suspension preferably in an aqueous solvent, but an organic coating composition may also be applied.

[0123] Examples of film-forming agents which are suitable for use in accordance with the present invention are agents selected from the group consisting of cellulose derivatives such as, e.g., ethylcellulose, cellulose acetate, cellulose propionate, cellulose butyrate, cellulose valerate, cellulose acetate propionate; acrylic polymers such as, e.g., polymethyl methacrylate; vinyl polymers such as, e.g., polyvinyl acetate, polyvinyl formal, polyvinyl butyryl, vinyl chloride-vinyl acetate copolymer, ethylene-vinyl acetate copolymer, vinyl chloride-propylene-vinyl acetate copolymer; silicon polymers such as, e.g., ladder polymer of sesquiphenyl siloxane, and colloidal silica; polycarbonate; polystyrene; polyester; coumarone-indene polymer; polybutadiene; and other high molecular synthetic polymers.

[0124] In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

[0125] In one preferred embodiment, the acrylic coating is an acrylic resin lacquer used in the form of an aqueous dispersion, such as that which is commercially available from Rohm Pharma under the tradename Eudragit®. In further preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the tradenames Eudragit® RL 30 D and Eudragit® RS 30 D, respectively. Eudragit® RL 30 D and Eudragit® RS 30 D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL 30 D and 1:40 in Eudragit® RS 30 D. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids. The Eudragit® RL/RS dispersions may be mixed together in any desired ratio in order to ultimately obtain a modified release formulation having a desirable dissolution profile. The most desirable modified release formulations may be obtained from a retardant coating based on Eudragit® NE 30D, which is a neutral resin having a molecular weight of 800,000.

[0126] The amount of coating applied is adapted so as to obtain a predetermined dissolution characteristic of the

fraction of the composition. The percentage by weight of the modified release coating on the individual pellet will, for the fraction providing the extended duration of effect of the NSAID substance, be at the most about 20% w/w on an average, such as, e.g. about 15% w/w, about 12% w/w, preferably at the most about 10% w/w on an average, more preferred in the range of about 3% to 6 % w/w on an average, based on the weight of the uncoated individual pellet. The amount of coating applied depends on the predetermined dissolution characteristics of the particular core composition and the desired release profile of the fraction.

[0127] However, the amount of coating applied should also be adapted so that there will be no rupturing problems.

[0128] The coating may be admixed with various excipients such as plasticizers, anti-adhesives such as, e.g., colloidal silicium dioxide, inert fillers, and pigments in a manner known *per se.*

[0129] Tackiness of the water-dispersible film-forming substances may be overcome by simply incorporating an anti-adhesive in the coating. The anti-adhesive is preferably a finely divided, substantially insoluble, pharmaceutically acceptable non-wetting powder having anti-adhesive properties in the coating. Examples of anti-adhesives are metallic stearates such as magnesium stearate or calcium stearate, microcrystalline cellulose, or mineral substances such as calcite, substantially water-insoluble calcium phosphates or substantially water-insoluble calcium sulphates, colloidal silica, titanium dioxide, barium sulphates, hydrogenated aluminium silicates, hydrous aluminium potassium silicates and talc. The preferred anti-adhesive is talc. The anti-adhesive or mixture of anti-adhesives is preferably incorporated in the coating in an amount of about 0.1-70% by weight, in particular about 1-60% by weight, and preferably about 8-50% by weight of the inner film layer. By selecting a small particle size of the talc, a larger surface area is obtained; the consequent higher anti-adhesive effect makes it possible to incorporate smaller amounts of specific anti-adhesives.

[0130] The individual modified release coated multiple-units may further comprise a middle coating between the "inner coat" and the "outer coat", Such coating may be adapted to stabilize the controlled release coated multiple-units and to prevent undesired changes of the release profile of each coated unit. Accordingly, the middle lacquer or coating may contribute to stability of the release profile of the dosage unit. Accordingly, the multiple units may further comprise an outer film layer.

[0131] In one aspect, the outer second layer comprises a water-based film-forming agent which prevents adhesion between the units at elevated temperatures and imparts flowability to the units, the water-based film-forming agent being anti-adhesive at temperatures above about 40 °C, especially temperatures above about 50 °C, such as a temperature between about 60 °C and about 120 °C, and being selected from diffusion coating materials such as ethylcellulose or enteric coating materials such as anionic poly(meth)acrylic acid esters, hydroxypropylmethylcellulosephthalate, cellulose-acetatephthalate, polyvinylacetatephthalate, polyvinylacetatephthalate-crotonic acid copolymerisates, or mixtures thereof, or water-soluble coating materials such as water-soluble cellulose derivatives, e.g. hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, propylcellulose, hydroxyethylcellulose, carboxyethylcellulose, carboxymethylhydroxyethylcellulose, hydroxymethylcellulose, carboxymethylethylcellulose, methylhydroxypropylcellulose or hydroxypropylmethylcellulose.

[0132] Examples of plasticizers for use in accordance with the present invention include triacetin, acetylated monoglyceride, rape oil, olive oil, sesame oil, acetyl tributyl citrate, acetyl triethyl citrate, glycerin, sorbitol, diethyloxalate, diethylmalate, diethylmaleate, diethylfumarate, diethylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacetate, triethylcitrate, tributylcitrate, glyceroltributyrate, polyethyleneglycol, propyleneglycol, 1,2-propyleneglycol, dibutylsebacate, diethylsebacate and mixtures thereof. The plasticizer is normally incorporated in an amount of less than 10% by weight, calculated on the dry matter content of the coating composition.

Pharmaceutically acceptable excipients

[0133] Apart from the active drug substance in the multiple units, the pharmaceutical composition according to the invention may further comprise pharmaceutically acceptable excipients.

[0134] In the present context, the term "pharmaceutically acceptable excipient" is intended to denote any material which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se.* A pharmaceutically acceptable excipient may be added to the active drug substance with the purpose of making it possible to obtain a pharmaceutical formulation which has acceptable technical properties. Although a pharmaceutically acceptable excipient may have some influence on the release of the active drug substance, materials useful for obtaining modified release are not included in this definition.

[0135] Fillers/diluents/binders may be incorporated such as sucrose, sorbitol, mannitol, lactose (e.g., spray-dried lactose, α-lactose, β-lactose, Tablettose®, various grades of Pharmatose®, Microtose or Fast-Floc®), microcrystalline cellulose (e.g., various grades of Avicel®, such as Avicel® PH101, Avicel® PH102 or Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tai® and Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low-substituted) (e.g. L-HPC-CH31, L-HPC-LH11, LH 22, LH 21, LH 20, LH 32, LH 31, LH30), dextrins, maltodextrins (e.g. Lodex® 5 and Lodex® 10), starches or modified starches (including potato starch, maize starch and rice starch), sodium chloride, sodium phosphate, calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate), calcium sulfate,

calcium carbonate. In pharmaceutical formulations according to the present invention, especially microcrystalline cellulose, L-hydroxypropylcellulose, dextrins, maltodextrins, starches and modified starches have proved to be well suited.

[0136] Disintegrants may be used such as cellulose derivatives, including microcrystalline cellulose, low-substituted hydroxypropyl cellulose (e.g. LH 22, LH 21, LH 20, LH 32, LH 31, LH30); starches, including potato starch; croscarmellose sodium (i.e. cross-linked carboxymethylcellulose sodium salt; e.g. Ac-Di-Sol®); alginic acid or alginates; insoluble polyvinylpyrrolidone (e.g. Polyvidon® CL, Polyvidon® CL-M, Kollidon® CL, Polyplasdone® XL, Polyplasdone® XL-10); sodium carboxymethyl starch (e.g. Primo-gel® and Explotab®).

[0137] Surfactants may be employed such as nonionic (e.g., polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85, polysorbate 120, sorbitane monoisostearate, sorbitanmonolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesquioleate, sorbitan tri oleate, glyceryl monooleate and polyvinylalkohol), anionic (e.g., docusate sodium and sodium lauryl sulphate) and cationic (e.g, benzalkonium chloride, benzethonium chloride and cetrimide) or mixtures thereof.

[0138] Other appropriate pharmaceutically acceptable excipients may include colorants, flavouring agents, and buffering agents.

[0139] In the following examples, the invention is further disclosed.

BRIEF DESCRIPTION OF THE DRAWING

[0140]

Figure 1 shows a target plasma profile for lornoxicam together with a profile for plain tablets and solutions used to estimate the target profile,

figure 2 shows target *in vivo* dissolution profile for lornoxicam once daily and plain tablets,

figure 3 shows dissolution profiles of lornoxicam compositions containing 8 mg of lornoxicam; further details are given in Examples 14 and 15 herein,

figure 4 shows dissolution profiles of compositions according to Example 15,

figure 5 shows dissolution profiles of compositions according to Example 17.

MATERIALS AND METHODS

[0141] Materials employed in the compositions which were investigated in the course of development of the present invention were as given in the following. In those cases where reference is given to an official pharmacopoeia, the reference is to the current edition of the stated pharmacopoeia.

The following abbreviations are used:

[0142]

Ph. Eur.	European Pharmacopoeia
USP/NF	United States Pharmacopoeia National Formulary
DLS	Dansk Lægemiddelstandard

Materials	Quality	Manufacturer
Cellulosum microcristallinum (Avicel PH 101)	Ph.Eur.	FMC
Polysorbate 20	Ph.Eur.	Henkel
Lactose monohydrate	Ph.Eur.	DMV
Carmellose sodium (Blanose 7 LFD)	Ph.Eur.	Aqualon
Maltodextrin (Glucidex 2)	USPNF	Roquette
Pregelatinised Starch (Starch 1500)	USPNF	Colorcon

(continued)

Materials	Quality	Manufacturer
Hypromellose (Methocel E 5 Premium)	Ph. Eur.	Dow
Magnesii stearas	Ph.Eur.	Akcros Chemicals
Talcum	Ph.Eur.	Whittaker, Clark and Daniels
Eudragit NE 30 D	Ph.Eur.	Röhm Pharma GmbH
Croscarmellose sodium (Ac-Di-Sol)	Ph.Eur.	FMC
Dibasic Calcium Phosphate, Anhydrous	USPNF	Kyowa
(Calcium hydrogen phosphate, mean particle size approx. 30 µm)		
Sodium bicarbonate	USPNF	Kirsch
(sodium hydrogencarbonate, mean particle size approx. 120 µm)		
Hydroxypropylcellulose (HPC L fine)	Ph. Eur.	Nippon Soda
Low-substituted Hydroxy Propyl Cellulose (LH21)	USPNF	Shin-Etsu
Ethanol, 96 %	DLS	Danisco
Aqua Purificata	Ph. Eur.	
Naproxen	Ph. Eur.	Syntex Pharm.
Polyvidone 30	Ph. Eur.	BASF
Isopropanol	Ph. Eur.	Sveda Kemi

[0143] Whenever relevant, the mean particle size was determined by employment of a Malvern laser particle size analyser.

[0144] In the following five different dissolution methods I-V are described. In the table below is given an overview of the important differences between the five methods:

Dissolution method	Dissolution medium	
	pH	volume
I	7.4	900 ml
II	0.07 N HCl	900 ml
III	0.1 N HCl/7.3[a]	750 ml of medium 1 and 250 ml of medium 2
IV	0.1 N HCl/7.4[b]	750 ml of medium 1; after 1 hour this medium is changed to 900 ml of medium 2
V	7.3	1000 ml

[a] 750 ml 0.1 N HCl is employed in the first 1 hour of the test and then 250 ml of a medium 2 is added leading to a resulting pH of the dissolution medium of 7.3

[b] 750 ml 0.1 N HCl is employed in the first 1 hour of the test and is then replaced by 900 ml of a medium 2 having a pH of 7.4

[0145] The various dissolution methods have been employed to show that the method chosen for determining the dissolution profile of various compositions has an influence on the result obtained, i.e. different dissolution profiles are obtained when employing different dissolution methods.

[0146] The dissolution methods given below give details partly with respect to the test method and partly with respect to the analysis method. The following methods are directed to compositions containing lornoxicam as an example of an NSAID substance; however, in the case of compositions containing other drug substances than lornoxicam the test methods and details with respect to procedure and preparation of reagents are the same apart from an adjustment of the analysis method and the drug substance included in the standard solutions to conditions which are suitable for the drug substance in question. A person skilled in the art will have no difficulties in selecting a suitable method of analysis for a specific drug substance.

DISSOLUTION METHOD I

pH 7.4 (lornoxicam)

Test method

[0147] Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

[0148] Glass fibre filter: Whatman GF/F

[0149] Dissolution medium: 900.0 ml dissolution medium pH 7.4

[0150] Number of revolutions: 50 rpm

[0151] Stirrer: Paddle

[0152] Temperature of dissolution medium: 37 °C ± 0.5 °C

[0153] Measuring times: Every 5 minutes after the start of the test (details appear from the following examples)

Analysis method

[0154]

Detection wavelength: λ = 378 nm
Measuring equipment: UV/VIS - spectrophotometer, 1 cm cuvette

Preparation of reagents

[0155] Dissolution medium: An aqueous solution containing 10.1 mg/ml of sodium hydrogenphosphate dihydrate (Na_2HPO_4 $2H_2O$) and 1.6 mg/ml and sodium dihydrogenphosphate monohydrate (NaH_2PO_4 H_2O); the pH of the dissolution medium is 7.4.

Standards

[0156] Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam are prepared. Lornoxicam is dissolved in solvent for standards given below.

[0157] Standards: 20.00 ml of each of the stock solutions are added to the reference vessel (cf. below).
Solvent for standards:1.5% w/w aqueous sodium acetate solution : methanol (1:1 v/v)

Test procedure

[0158] 900 ml of the dissolution medium are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C ± 0.5 °C. The product to be tested (e.g. a granulate, pellets, a final composition) is placed in the vessels, and the spindel is started. In the last vessel, 20.0 ml of each of the stock solutions are added. The absorbance of the samples and standards is measured at 378 nm with a zero setting towards the dissolution medium.

[0159] The percentage dissolved is measured over a suitable time interval.

DISSOLUTION METHOD II

0.07 HCl (lornoxicam)

[0160] Lornoxicam has a very low solubility in 0.1 N HCl *inter alia* in order to show that the relatively fast release fraction indeed releases lornoxicam at acidic pH (simulating the pH conditions in the stomach), dissolution method II is employed.

Test method

[0161] Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using

Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 900.0 ml dissolution medium

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring time: Every 5 minutes after the start of the test (details appear from the following examples)

Analysis method

[0162]

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS - spectrophotometer, 1 cm cuvette

Preparation of reagents

[0163] Dissolution medium: Weigh out 50.0 g of sodium chloride and measure out 141.6 ml of concentrated hydrochloric acid. Dissolve the chemical with distilled water and dilute to 25 l with distilled water.

Standards

[0164] Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lomoxicam were prepared. Lomoxicam is dissolved in solvent for standards (cf. below).
[0165] Standards: 20.00 ml of each of the stock solutions is added to the reference vessel (cf. below).
[0166] Solvent for standards: 1.5% w/w aqueous sodium acetate solution : methanol (1:1 v/v)

Test procedure

[0167] 900 ml of dissolution medium are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C ± 0.5 °C. The product to be tested (e.g. a granulate, pellets or a final composition) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindel is started, and the absorbance of the samples and standards is measured at 378 nm with zero setting towards the dissolution medium.
[0168] The percentage dissolved is measured over a suitable time interval.

DISSOLUTION METHOD III

0.1 N HCl / pH 7.3 (lomoxicam)

[0169] This dissolution method includes a change in pH to simulate the *in vivo* situation.

Test method

[0170] Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

[0171]

Dissolution medium: 750 ml of dissolution medium 1, after 1 hour 250 ml of dissolution medium 2 are added

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring times: Every 5 minutes after the start of the test (details appear from the following examples)

Analysis method

[0172]

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS - spectrophotometer, 1 cm cuvette

Preparation of reagents

[0173]

Dissolution media
Dissolution medium 1: 0.1 N HCl

[0174] Dissolution medium 2: Weigh out 73,6 g trisodium phosphate, dodecahydrate (Na_3PO_4, $12H_2O$) and measure out 31,8 ml 0,1 N sodium hydroxide. Dissolve the chemicals in distilled water and dilute to 1000.0 ml with distilled water.

Standards

[0175] Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).
[0176] Standards: 20.00 ml of each of the stock solutions are added to the reference vessel (cf. below).
[0177] Solvent for standards:1.5% w/w aqeous sodium acetate solution : methanol (1:1 v/v)

Test procedure

[0178] 750 ml of dissolution medium 1 are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C ± 0.5 °C. The product to be tested (e.g. a granulate, pellets or a final composition) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindel is started. After 1 hour 250 ml of dissolution medium 2 (37 C° ± 0.5 °C) are added.
[0179] The absorbance of the samples and standards is measured at 378 nm with zero setting towards the dissolution medium.
[0180] The percentage dissolved is measured over a suitable time interval.

DISSOLUTION METHOD IV

0.1 N HCl / pH 7.4 (lornoxicam)

[0181] This dissolution method includes a change in pH to simulate the *in vivo* situation. Furthermore, this dissolution method has been employed in experiments performed in order to clarify whether a pre-treatment of the product in 0.1 N hydrochloric acid has any influence on the results obtained afterwards in a dissolution medium having a pH of 7.4.

Test method

[0182] Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 750 ml of dissolution medium 1, after 1 hour the medium is changed to 900 ml of dissolution medium 2.

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring times: Every 5 minutes after the start of the test (details appear from the following examples)

Analysis method

[0183]

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS - spectrophotometer, 1 cm cuvette

Preparation of reagents

[0184]

Dissolution media:

Dissolution medium 1: 0.1 N HCl

[0185] Dissolution medium 2: Distilled water containing 10.1 mg/ml of sodium hydrogenphosphate dihydrate (Na_2HPO_4 $2H_2O$) and 1.6 mg/ml of sodium dihydrogenphosphate monohydrate (NaH_2PO_4 H_2O)

Standards

[0186] Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).

[0187] Standards: 20.00 ml of each of the stock solutions is added to the reference vessel (cf. below)

[0188] Solvent for standards: 1.5% w/w aqueous sodium acetate solution : methanol (1:1 v/v)

Test procedure

[0189] 750 ml of dissolution medium 1 are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C ± 0.5 °C. The product to be tested (e.g. a granulate, pellets or a final composition) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindel is started. After 1 hour the medium is decanted carefully and the medium is discarded. To the remaining product in the vessel 900 ml of dissolution medium 2 (37 °C ± 0.5 °C) are added. The absorbance of the samples and standards is measured at 378 nm with zero setting towards the dissolution medium employed.

[0190] The percentage dissolved is measured over a suitable time interval.

DISSOLUTION METHOD V

pH 7.3 (lornoxicam)

[0191] This dissolution method was used to *inter alia* clarify the influence of pH and/or the specific dissolution medium on the release rate and also to clarify, if the results obtained at pH 7.3 - without any pre-treatment in 0.1 N hydrochloric acid - were different from those obtained with pre-treatment in 0.1 N hydrochloric acid.

[0192] The buffer capacity of the dissolution medium employed was investigated to ensure a sufficient capacity. pH in the medium was measured before a product was added and after the end of the test. Both measurements revealed the same pH value (7.28), i.e. the buffer capacity is sufficient.

Test method

[0193] Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

[0194]

Dissolution medium: 750 ml of the dissolution medium 1 and 250 ml of dissolution medium 2, the resulting pH is 7.3

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring times: Every 5 minutes after the start of the test (details appear from the following examples)

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS - spectrophotometer, 1 cm cuvette

Preparation of reagents

Dissolution media:

[0195]

Dissolution medium 1: 0.1 N HCl

Dissolution medium 2: Weigh out 73,6 g trisodium phosphate dodecahydrate (Na_3PO_4 $12H_2O$) and measure out 31,8 ml 0,1 N sodium hydroxide. Dissolve the chemicals in distilled water and dilute to 1000,0 ml with distilled water.

Standards

[0196] Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).

[0197] Standards: 20.00 ml of each of the stock solutions is added to the reference vessel (cf. below).

[0198] Solvent for standards: 1,5 % sodium acetate solution : methanol (1:1)

Test procedure

[0199] 750 ml of the dissolution medium 1 and 250 ml of dissolution medium 2 are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C ±

0.5 °C. The product to be tested (e.g. a granulate, pellets or a final composition) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindel is started. The absorbance of the samples and standards is measured at 378 nm with zero setting towards the dissolution medium.

[0200] The percentage dissolved is measured over a suitable time interval.

Calculation for all methods

[0201] Percentage dissolved was calculated with reference to an external standard in the reference vessel.

[0202] The concentration of the standard in the reference vessel is calculated by the formula below:

$$\text{mg lornoxicam per 1000 ml} = \left(\frac{q_1 \bullet 20}{V} + \frac{q_2 \bullet 20}{V}\right) \bullet \frac{1000}{940}$$

[0203] Where:

q_1 = amount of standard weighed out for S_1 (mg)
q_2 = amount of standard weighed out for S_2 (mg)
20 = added volume of S_1 and S_2 to the reference vessel (ml)
V = dilution volume of the standard (ml)
940 = volume in the reference vessel after addition of the standards (S_1 and S_2) to the vessel (ml)
1000 = conversion factor to 1000 ml

[0204] The content of lornoxicam as percentage dissolved was calculated from the formula below:

$$\frac{abs_{sample} \cdot StA \cdot V \cdot 100}{abs_{StA}\ 1000 \cdot u} \cdot \frac{n}{100}$$

Where

abs_{sample} = absorbance measured in each vessel containing samples
StA = mg lornoxicam pr 1000 ml in the vessel containing standard
V = volume of the medium (ml)
100 = factor converting to percent
abs_{StA} = absorbance measured in vessel containing the standard
u = declared content (mg)
n = potency of the standard (%)
100 = factor converting to percent
1000 = factor converting the concentration of the standard to mg/ml

[0205] The following examples are intended to illustrate specific embodiments of the present inventions but are not intended in any way to limit the invention.

EXAMPLES

[0206] The following Examples 1 - 8 relate to the preparation of various cores containing lornoxicam as an example of an NSAID substance. Example 9 relates to the preparation of a quick release granulate, Examples 10-17 illustrate *inter alia* the influence of the composition of the pellets or the coat on the release rate and Example 18 relates to an immediate release composition disclosed in EP-A-0 438 249.

EXAMPLE 1

Preparation of cores containing lornoxicam and coating of the cores with a CR coating

[0207] Batch Nos. 04029831 (uncoated pellet cores) and 05029833 (coated pellet cores) were prepared.

[0208] Lornoxicam pellet cores were prepared by manufacturing of pellet cores and subsequent coating with an inner and an outer coat.

[0209] The pellet cores were prepared by the use of an extrusion/spheronization technique.

[0210] The ingredients are listed in Table 1. The ingredients I and II were mixed in a beaker by stirring, wetted with 150 g water and then mixed to a homogenous mass. The ingredients III to VII were filled into a Moulinex laboratory size mixer and mixed for 5 min, whereafter the homogenous mass was added and mixed. The beaker was rinsed with the remaining water and added to the mixer.

Table 1

	Ingredients	Amount (g):
I	Lornoxicam	54
II	Polysorbate 20	54
III	Cellulose, microcrystalline	102
IV	Lactose	315
V	Carmellose sodium	3
VI	Maltodextrin	12
VII	Pregelatinized starch	60
VIII	Purified water	150 + 18

[0211] The resulting mass was extruded in a Nica E 140 extruder with a screen size of 0.6 mm. The extrudate was spheronized in a laboratory size spheronizer at a rotation speed of 700 rpm for 4 min. The pellet cores thus produced were dried in a laboratory size fluid bed dryer with an inlet temperature of approximately 40° C, and the drying process was continued until the outlet temperature has reached approximately 30° C. The total drying time was approximately 25 min.

[0212] The dried pellet cores were fractionated in a Retsch sieving apparatus with a lower screen of 0.5 mm and an upper screen of 0.8 mm.

[0213] The release of lornoxicam from the pellet cores obtained was determined by dissolution method I (pH 7.4) and is as follows:

Time	Release (%)
10 min.	52.1
1 h	97.6

[0214] Thus, the relase of lornoxicam from the uncoated pellets is rapid and is almost accomplished within about 1 hour.

[0215] 100 g of these pellet cores were coated with an inner coat and an outer coat in a laboratory size bottom spray fluid bed coater with a spray pressure of 1 bar for both the inner coat and the outer coat. The temperature of the coating process was maintained at an inlet temperature of approximately 35° C to 40° C.

[0216] The composition of the coating is shown in Table 2:

Table 2

Ingredient	Amount (g)
Inner coat	
Hypromellose (Methocel E prem)	3.25
Magnesium stearate	0.68
Talc	6.07
Eudragit NE 30 D	216
Purified water	274
Outer coat	
Hypromellose (Methocel E5 prem)	4.0
Talc	4.0
Purified water	96.0

[0217] In the coating process the following amount of inner and outer coat was applied. The amount of dry matter applied calculated in percentage of the pellet core weight also appears from the below:

Inner coat: 35.9 g coating solution (corresponding to a dry matter content of approximately 5.5% w/w of the pellet core weight)
Outer coat: 12.5 g coating solution (corresponding to a dry matter content of approximately 1 % w/w of the pellet core weight)

[0218] After the application of the coatings, the coated pellet cores were cured at a bed temperature of approximately 70° C for 30 min, whereafter the coated pellet cores were cooled to a bed temperature below 35° C.

[0219] After the coating, the coated pellet cores are screened through a 1.2 mm screen. Oversized material is discarded.

EXAMPLE 2

Preparation of pellet cores according to the invention leaving out a surface active substance from the cores

[0220] Batch No. 09029831 (uncoated pellet cores) was prepared.

[0221] Lornoxicam pellet cores were prepared by using the ingredients listed in Table 3.

Table 3

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Cellulose,microcrystalline	54
III	Lactosemonohydrate	216
IV	Carmellosesodium	3
V	Purified water	84

[0222] The pellet cores were prepared by the use of the extrusion/spheronization technique as described in Example 1, wherein the ingredients I to IV were mixed for 5 min in a Moulinex laboratory size mixer, whereafter the ingredients V was added.

[0223] The release of lornoxicam from pellet cores was determined by dissolution method I (pH 7,4) and is as follows:

Time	Release (% w/w)
10 min	19.1
1 h	69.8

[0224] From the dissolution data given above it is seen that the release is not accomplished after 1 hour and compared with the result obtained with the uncoated pellet cores in Example 1 it seems as if the inclusion of a surface active agent like e.g. polysorbate 20 has a significant influence on the dissolution rate.

EXAMPLE 3

Preparation of pellet cores corresponding to the pellets in Example 1 but in a smaller batch size

[0225] Batch No. 09029832 (uncoated pellet cores) was prepared.

[0226] This Example is intended to illustrate any relevant variation which may turn up as a dependency of the batch size.

[0227] Lornoxicam pellet cores were prepared as described in Example 1 with the exception that in Example 3, the amounts of the ingredients listed in Table 4 were used.

Table 4

	Ingredients	Amount (g)
I	Lornoxicam	27

Table 4 (continued)

	Ingredients	Amount (g)
II	Polysorbate 20	27
III	Cellulose, microcrystalline	51
IV	Lactose	157.5
V	Carmellose sodium	1.5
VI	Maltodextrin	6
VII	Pregelatinized starch	30
VIII	Purified water	60 + 15

[0228] The release of lornoxicam from these pellets cores was determined by dissolution method I (pH 7.4) and is as follows:

Time	Release (% w/w)
10 min	61.2
1 h	98.0

[0229] Thus, the pellet cores prepared have the same dissolution behaviour as the pellet cores prepared in Example 1, i.e. the batch size seems to be without any significant influence on the release rate.

EXAMPLE 4

Preparation of coated pellet cores having a thinner inner coating than the coated pellet cores of Example 1

[0230] Batches Nos. 11029831 (uncoated pellet cores) and 20029832 (coated pellet cores) were prepared.

[0231] Lornoxicam pellet cores were prepared as described in Example 1 with the exception that in Example 4, the amounts of the ingredients listed in Table 5 were used.

Table 5

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Polysorbate 20	27
III	Cellulose, microcrystalline	51
IV	Lactose	157.5
V	Carmellose sodium	1.5
VI	Maltodextrin	6
VII	Pregelatinized starch	30
VIII	Purified water	51 + 15

[0232] The release of lornoxicam from these pellets cores was determined by dissolution method I (pH 7.4) and is as follows:

Time	Release (% w/w)
10 min	63.8
1h	100.7

[0233] Accordingly, the release of lornoxicam from the pellet cores is accomplished within 1 hour.

[0234] The pellet cores were coated as described in Example 1 with the exception that in Example 4, 100 g pellet cores were coated with an amount of inner and outer coat as follows:

Inner coat: 20.0 g coating solution (corresponding to a dry matter content of approximately 3% w/w of the pellet core weight).

Outer coat: 12.5 g coating solution (corresponding to a dry matter content of approximately 1 % w/w of the pellet

core weight).

[0235] As appears from the above, the amount of dry matter of the inner coat is smaller than in Example 1, whereas the amount of dry matter of the outer coat is the same as in Example 1. Accordingly, it is expected that the release of lornoxicam from the coated pellets of Example 4 is faster than that of lornoxicam from the coated pellets of Example 1.

EXAMPLE 5

Preparation of pellet cores corresponding to those of Example 3 with the exception that the surface active agent is replaced by lactose

[0236] Batch No. 11029834 (uncoated pellet cores) was prepared.

[0237] Lornoxicam pellet cores were prepared as described in Example 2 with the exception that in Example 5, the ingredients listed in Table 6 were used. Compared with the above Example 3 it is seen that the composition of pellet cores of Example 5 is very similar to those of Example 3, the only differences are that in the pellet cores of Example 3 a surface active agent (polysorbate 20) is included and the amount of water employed differs a little.

Table 6

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Cellulose, microcrystalline	51
III	Lactose	184.5
IV	Carmellose sodium	1.5
V	Maltodextrin	6.0
VI	Pregelatinized starch	30.0
VII	Purified water	84.0

[0238] The release of lornoxicam from these pellets cores were determined by dissolution method I (pH 7.4) and is as follows:

Time	Release (% w/w)
10 min	20.5
1h	62.4

[0239] In conclusion the same pattern is observed as in Example 2, namely that the exclusion of a surface active agent has a decreasing effect on the release rate of lornoxicam from the pellet cores.

EXAMPLE 6 (Comparative)

Preparation of pellet cores having a content of a disintegrant

[0240] Batch No. 19029834 (uncoated pellet cores) was prepared.

[0241] lornoxicam pellet cores were prepared by using the extrusion/spheronization technique as described in Example 1. However, the ingredients used in Example 6 are listed in Table 7:

Table 7

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Polysorbate 20	27
III	Cellulose, microcrystalline	51
IV	Lactose	142.5
V	Carmellose sodium	1.5
VI	Maltodextrin	6
VII	Pregelatinized starch	30

Table 7 (continued)

	Ingredients	Amount (g)
VIII	Croscarmellose sodium	15
IX	Purified water	51 + 15 + 15

[0242] The ingredients I and II were mixed in a beaker, wetted with 51 g water and then mixed to a homogeneous mass. The ingredients III to VIII were added to a Moulinex laboratory size mixer and mixed for 5 min, whereto the homogeneous mass was added and mixed. The beaker was rinsed with 2 x 15 g water and added to the mixer.

[0243] The extrudation and spheronizing procedure were performed as described in Example 1.

[0244] The release of lornoxicam from the pellet cores was determined by dissolution method II (0.07 N HCl) and is as follows:

Time	Release (% w/w)
1h	5.7

[0245] Thus, only a very small amount of the lornoxicam present in the pellets is released at a pH corresponding to that of 0.07 N HCl. The inclusion of an disintegrant such as, e.g., croscarmellose sodium does not seem to have any increasing effect on the release rate of lornoxicam from the pellet cores. Furthermore, uncoated cores containing lornoxicam do not seem to be a suitable choice in order to obtain a relatively fast release of lornoxicam at low pH like the conditions in the stomach.

EXAMPLE 7 (Comparative)

Preparation of pellet cores - modification of the composition of the pellets in order to influence the release rate of lornoxicam

[0246] Batch No. 19029836 (uncoated pellet cores) was prepared.

[0247] Lornoxicam pellet cores were prepared. The ingredients used are listed in Table 8.

Table 8

	Ingredients	Amount (g)
I	Lornoxicam	7.5
II	Sodium bicarbonate	37.7
III	Cellulose, microcrystalline	90.4
IV	Dibasic Calcium Phosphate, Anhydrous	104.1
V	Low-substituted Hydroxypropyl Cellulose	45.3
VI	Hydroxypropylcellulose	15
VII	Purified water	115.8
VIII	Ethanol 99.9 %	38.7

[0248] The ingredients II to IV were mixed in a Moulinex laboratory size mixer and mixed for 5 min. To 100 g of this mixture ingredient I was added and mixed in a cubus mixer for 5 min. The resulting mass was screened through a 0.5 mm screen and returned to the Moulinex mixer and mixed for further 6 min. A premixed mixture of ingredient VII and VIII was added to the powder mixture and massed for 6 min.

[0249] The resulting mass was then extruded and spheronized according to the method described in Example 1.

[0250] The release of lornoxicam from the pellet cores was determined by dissolution method II (0.07 N HCl) and is as follows:

Time	Release (% w/w)
After 1h	37.8

[0251] The release of lornoxicam from the pellets is significantly increased compared with the pellets of Example 6, but still not quite satisfactory.

EXAMPLE 8

Preparation of pellets coated with a coating having varying amounts of a hydroxypropylmethylcellulose (HPMC)

Batch No. 23029833 (uncoated pellets) was prepared

[0252] Lornoxicam pellet cores were prepared as described in Example 4 and with the same composition.

[0253] The release of lornoxicam from the pellet cores was determined by dissolution method III (0.1 N HCl followed by pH 7.3) for 3 hours (i.e. 1 hour at a pH corresponding to the pH of 0.1 N HCl and 2 hours at pH 7.3) and is as follows:

Time	Release (% w/w)
10 min	36.9
1h	37.2
1 + 1 h:	86.4
1 + 2h:	95.7

[0254] Thus, the release in 0.1 N HCl is not very high (most of the lornoxicam which releases in 0.1 N HCl is released within the first 10 min) and the release rate is certainly not fast enough to anticipate that lornoxicam is released *in vivo* sufficiently fast to lead to a therapeutic effect.

[0255] In the following, two different batches of coated pellets of 100 g each were prepared.

[0256] Batch 1 (Batch No. 24029832 - coated pellet cores) :

[0257] 100 g pellet cores were coated according to the procedure described in Example 1. The composition of the coating is as follows:

Ingredients	Amount (g)
Inner coat	
Hypromellose (Methocel E5 prem)	11.3
Magnesium stearate	0.6
Talc	5.4
Eudragit NE 30 D	191.7
Purified water	291
Outer coat	
Hypromellose (method E% prem)	4.0
Talc	4.0
Purified water	96.0

[0258] The following amount of inner and outer coat was used:

Inner coat: 20.1 g coating solution (corresponding to a dry matter content of approximately 3% w/w of the pellet core weight; the HPMC content corresponds to 15.1% w/w).
Outer coat: 12.5 g coating solution (corresponding to a dry matter content of approximately 1 % w/w of the pellet core weight).

[0259] Batch 2 (Batch No.. 26029832 - coated pellet cores):

[0260] 100 g pellet cores were coated as described in Example 1. The composition of the coating is as follows:

Ingredients	Amount (g)
Inner coat	
Hypromelose (Methocel E5 prem.)	3.74
Magnesium stearate	0.17
Talc	1.48

(continued)

Ingredients	Amount (g)
Inner coat	
Eudragit NE 30 D	31.9
Purified water	62.7
Outer coat	
Hypromellose (method E% prem)	4.0
Talc	4.0
Purified water	96.0

[0261] The following amount of inner and outer coat was used:

Inner coat: 20.1 g coating solution (corresponding to a dry matter content of approximately 3% w/w of the pellet core weight; the HPMC content corresponds to 25% w/w).
Outer coat: 12.5 g coating solution (corresponding to a dry matter content of approximately 1 % w/w of the pellet core weight).

EXAMPLE 9

Preparation of a quick release granulate containing lornoxicam

Batch No. 972510 (granulate) was prepared.

[0262] A granulate containing lornoxicam were prepared by using the ingredients listed in Table 9. The composition of the granulate is essentially the same as that of the pellet cores of Example 7. The granulate was prepared in order to investigate whether it is possible to achieve a faster release of lornoxicam from a granulate than from pellet cores. From the results given below it is seen that the step of preparing pellets from a particulate composition containing lornoxicam has a dramatically decrease on the release rate of lornoxicam from the composition.

Table 9

	Ingredients	Amount (kg)
I	Lornoxicam	2.00
II	Sodium hydrogencarbonate	10.00
III	Cellulose microcristalline	24.00
IV	Calcium hydrogen phosphate anhydrous	27.60
V	Hydroxy Propyl Cellulose	4.00
VI	Low-Substituted Hydroxy Propyl Cellulose	12.00
VII	Purified water	27.00
VIII	Ethanol 96 %	9.00
IX	Calcium stearate	0.40

[0263] Ingredients II, III IV, V and VI were added to a Diosna intensive mixer and mixed for 1 min with the impeller speed I and chopper speed I. Out of this mixture, 10 kg was added the ingredient I by sieving through a Quadro Comil U20 with the sieve 062R in the following way: A part of the 10 kg mixture was sieved followed by ingredient I, whereafter the remaining of the 10 kg mixture was sieved. Ingredient I was not added to the mixture and mixed in the Diosna mixer for approximately 1 min.

[0264] A mixture of ingredient VII and VIII was added to the Diosna mixer, whereafter the granulation was started for 6 min with impeller speed I and with no use of the chopper.

[0265] After the granulation, the granulate was dried in a fluid bed until the outlet temperature had reached approximately 50°C and water content was below 1.0%, determined as LOD (Loss on Drying) when a sample of approximately 10 g was heated to a temperature of 70°C in 30 min. The granulate was sieved through a 0.71 sieve using a Frewitt siever. Oversized material was discarded.

[0266] Ingredient IX was sieved in the Quadro Comil with a sieve 062R and an equal amount of the granulate de-

scribed above was added and mixed. This mixture was mixed with the remaining of the granulate in the Diosna mixer for 25 sec with an impeller speed of I and without using the chopper.

[0267] This mixture was compressed into a 9,5 mm concave tablets with a hardness of 80 to 100 N (the compression of the granulate was performed in order to avoid any of the problems which could arise during dissolution testing of a granulate and which are related to such bad wetting properties of a granulate that the granulate would float on the top of the dissolution medium giving rise to a *in vitro* unsatisfactory release of lornoxicam. However, later results have shown that granulates prepared in accordance with the above have suitable wetting properties, i.e. the final step of compression before dissolution testing is not necessary.

[0268] The dissolution of tablet cores was determined by the dissolution method II (0.07 N HCl) and is as follows:

Time	Release (% w/w)
20 min	100.6

[0269] The disintegration time of the tablets tested was at the most about 5 min. Thus, the dissolution rate of the granulate is expected to be of the same or quicker order of magnitude.

[0270] The release data given above are most surprising and give evidence that a fast release fraction containing a drug substance which is almost insoluble under acidic conditions can only be obtained if the composition is designed to a very fast release. In other words, application of traditionally prepared granulates and/or compositions made from such traditional granulates or particulate formulations do not seem to release the drug substance sufficiently fast under acidic conditions as those prevailing in the stomach. Accordingly, such traditional compositions are expected to release only a minor amount of the drug substance in the stomach and to release the remaining amount of lornoxicam in the intestines, i.e. after the composition reaches the intestines 1-3 hours after intake.

[0271] Compared with the dissolution data given in Example 7 a dramatically increase in dissolution rate is observed for the granulate compared with the pellet cores. Thus, in order to achieve a very fast release of lornoxicam from a composition it seems as if the fast fraction advantageously may be constituted by a granulate rather than uncoated pellet cores or film-coated pellet cores.

Conclusion with respect to Examples 1-9

[0272] In the preceding examples it has been shown that pellets cores cannot release lornoxicam very quickly at pH 7,4 unless a surfactant is added (Examples 2 and 5), even though lornoxicam is soluble at pH 7,4. When a surfactant, e.g. polysorbate 20, was added the release at pH 7,4 was acceptable from the point of view that the core can enter an once daily formulations without significantly controlling the dissolution rate (Examples 1, 3 and 4). This control should ideally be taken care of by the applied lacquer.

[0273] When these pellet cores were analyzed with respect to dissolution behaviour under acidic conditions in which lornoxicam is only slightly soluble a satisfactory release was not obtained even if a surfactant was used (Examples 6 and 8). Therefore, another kind of subunits have to be used for the relatively fast releasing fraction. Subunits in the form of a granulate and with the composition as described in Example 9 seem to give a satisfactory fast release. However, subunits with the same formulation as in Example 9, but in the form of pellet cores, will not give a satisfactory release rate in acidic conditions as shown in Example 7.

EXAMPLE 10 (Comparative)

Preparation of a composition containing a mixture of uncoated and coated pellet cores

[0274] The following example illustrate the dissolution behaviour of a composition containing a mixture of uncoated and coated pellet cores. The uncoated pellets are intended to simulate a fast release fraction and the coated pellets are intended to simulate a delayed release fraction.

[0275] Coated pellets obtained according to Example 1 were mixed with pellet cores obtained according to Example 4 and the final composition contained 40% of uncoated pellet cores and 60% coated pellets (the percentage is given as % w/w of the total dose of lornoxicam in the composition, i.e. the uncoated fraction accounts for 40% w/w of the total content of lornoxicam whereas the coated fraction accounts for 60% w/w of the total content of lornoxicam. A unit dosage form of the composition contains 8 mg of lornoxicam.

[0276] The dissolution test was carried out according to dissolution method III. The following dissolution data were obtained:

Time (h)	11029831 (uncoated fraction) + 05029833 (coated fraction) (5.5/4.3)[a] Release (% w/w)
0	0
0.5	1.4
1	2.9
2	38.4
3	46.1
4	49.6
5	53.5
6	55.9
7	59
8	61.4
9	64.6
10	67.2
11	69.2
13	74
14	75.6
15	77.9
16	79.3
17	80.7
18	82.5
19	83.6
20	85.3
21	86.4
22	87
23	88.1
24	89

[a] (5.5/4.3) relates to the fact that the content of dry matter in the coat is 5.5% w/w and the HPML content is 4.3% w/w.

[0277] From the data given above it is seen that only 2.9% w/w lornoxicam is released after 1 hour. Thus, the "fast release fraction", i.e. the uncoated pellets, is not able to release all its content of lornoxicam under acidic conditions and during the first hour of the test. If this was the case, a release of about 40% is to be expected after 1 hour.

[0278] A dramatically increase in dissolution is observed after 2 hours reflecting the pH change of the dissolution medium 1 hour after the start of the test. Furthermore, a retardation of the release of lornoxicam is observed at pH 7.4 compared with the uncoated pellets cores, i.e. the coating is in control of the release rate. However, a composition containing a mixture of uncoated and coated pellets does not seem to enable a fast release of lornoxicam. Therefore, the fast release fraction has to been manipulated in some way in order to release the active substance (lornoxicam) faster).

EXAMPLE 11

Preparation of a composition containing a mixture of a quick release granulate and a delayed release fraction of coated pellet cores

[0279] The composition described below was prepared in order to investigate the influence on the overall release rate of the granulate prepared in Example 9 which seems to have favourable properties with respect to a quick and very fast release of lornoxicam even under acidic conditions.

[0280] Coated pellets obtained according to Example 4 were mixed with a granulate obtained according to Example 9, where the mixture contained 40% w/w of the total dose of lornoxicam in the form of the granulate and the remaining 60% w/w of the total dose of lornoxicam was in the form of coated pellets (the concentration of lornoxicam in the granulate is about 2-3 % w/w and about 9% w/w in the uncoated pellets). The dissolution test was carried out according to dissolution method III. The following dissolution data was obtained:

Time (h)	972510 (granulate) + 20029832 (coated pellets) (3/4.3) Release (% w/w)
0	0
1	37.2
2	41.3
3	44.6
4	48.2
5	51.3
6	53.9
7	57
8	59.6
9	61.8
10	64.7
11	66.9
12	69.4
13	71.6
14	73.6
15	75.7
16	77.6
17	79.5
18	81.2
19	82.9
20	84.4
21	86
22	87.4
23	88.5
24	89.8

[0281] From the dissolution data given above, a fast release of lornoxicam is observed which is ascribed to the influence of the lornoxicam granulate.

[0282] In contrast to the results obtained in Example 10 a release of about 40% w/w of lornoxicam is observed after 1 hours. Thus, the above example gives evidence that a manipulation of the composition of the fast release fraction is necessary in order to achieve a suitable release even at a low pH. Furthermore, a delayed release is observed with respect to the coated pellets fraction.

EXAMPLE 12

Investigation of the controlled release lacquer composition on the overall dissolution rate

[0283] Coated pellets obtained according to Example 8 (batch 1, 15% w/w HPMC in the coat was mixed with granulate obtained according to Example 9. The mixture contained 40% w/w of the total dose of lornoxicam in the form of the granulate, whereas the remaining 60% w/w of lornoxicam was in the form of coated pellets. The dissolution test was carried out according to dissolution method III. The following dissolution data was obtained:

Time (h)	972510 (granulate) + 24029832 (coated pellets) (3/15.1) Release (% w/w)
0	0
0.5	35.7
1	35.7
2	43.2
3	50.0
4	55.8
5	60.9
6	66.2

(continued)

Time (h)	972510 (granulate) + 24029832 (coated pellets) (3/15.1) Release (% w/w)
7	70.7
8	74.4
9	78.3
10	81.5
11	84.8
12	87.3
13	89.3
14	91.1
15	92.6
16	93.8
17	95.0
18	95.9
19	96.6
20	97.2
21	97.5
22	97.8
23	98.0
24	97.5

[0284] From the dissolution data given above a much faster release of the delayed release fraction is observed compared with the results obtained in Example 11. Thus, the composition of the coat can be adjusted to a suitable release rate. In this example the content of HPMC in the coat is 15.1% w/w.

EXAMPLE 13

Investigation of the influence of the composition of the controlled release coat on the release rate

[0285] Coated pellets obtained according to Example 8 (batch 2) were mixed with a granulate obtained according to Example 9. The mixture contained 40% w/w of the lornoxicam content in the form of the granulate and the remaining 60% w/w in the form of coated pellets. The dissolution test was carried out according to dissolution method III.

[0286] The following dissolution data was obtained:

Time (h)	972510 (granulate) + 26029832 (coated pellets) (3/25.0) Release (% w/w)
0	0
0.5	37.3
1	37.3
2	58
3	69.1
4	79.9
5	87.6
6	92.6
7	95.9
8	97.8
9	98.9
10	99.3
11	99.4
12	99.4
13	99.4
14	99.4
15	99.5

[0287] After 6 hours 92.6% w/w is released whereas only 69.4% w/w was released in Example 12. Thus, the increase of the concentration of HPMC in the coat (25% in the present example in contrast to 15% in Example 12) has an increasing effect on the release rate of lornoxicam from the composition.

EXAMPLE 14

Determination of release rate of lornoxicam from controlled release pellets

[0288] Dissolution data from coated pellets from Examples 1, 4 and 8 (batches 1 and 2) were determined by dissolution method I (pH 7.4). The following data have been obtained.

Time (h)	05029833 (coated pellets) (5.5/4.3) Example 1	20029832 (coated peltets) (3.0/4.3) Example 4	24029832 (coated pellets) (3.0/15.1) Example 8, batch 1	26029832 (coated pellets) (3.0/25.0) Example 8, batch 2
0	0	0	0	0
0.5	6.9	10.1	17.3	32.7
1	12.1	16.9	29	52.6
2	20.3	28.5	49.5	82.1
3	28.1	39.7	67.2	96.9
4	35.4	50	81.6	101.9
5	42	58.9	91.5	102.9
6	49.1	69.1	98.5	103
7	55.2	76.2	102.1	103.2
8	60.7	82.2	103.9	102.9
9	65.6	86.9	104.8	102.9
10	69.9	90.5	105.2	103.1
11	73.7	93.4	105.5	102.9
12	77.2	93.4	105.5	
13	80.3	95.2	105.8	
14	82.6	97.7	105.5	
15	85	97.9	105.8	
16	87.1	98	105.8	
17	88.6	98.7	105.9	
18	89.9	98.8	105.9	
19	91.2	99	105.8	

[0289] The data are also presented in Figure 3. Comparison of the results obtained from the composition of Example 1 with that of Example 4 illustrates that the thickness of the CR (controlled release) coat influences the release rate in such a manner that a thinner coat leads to a more rapid release. The influence of HPMC as an example of a substance which is capable of forming pores in the coat on the release rate is illustrated by the release rate of the two different batches of Example 8 and the results reveal an increasing release rate when the concentration of HPMC increases.

Conclusion with respect to Examples 10-14

[0290] In Examples 10-14, the preparation of a composition containing two fractions of subunits has been presented. One fraction representing a quick release part and the other fraction representing a controlled and delayed release part. Furthermore, the Examples illustrate the influence on the release rate of i) the composition of the quick release fraction and ii) composition and amount of lacquer applied on the controlled release fraction.

EXAMPLE 15

Investigation of the influence of the dissolution medium on the release rate

[0291] Dissolution data from coated pellets from Examples 4 and 8 (batch 2) were obtained using dissolution method V (pH 7.3), and are as follows:

Time (h)	20029832 (coated pellets) (3.0/4.3)[7.3] Example 4	26029832 (coated pellets) (3.0/25.0)[7.3] Example 8, batch 2
0	0	0
0.5	6.2	22
1	10.1	36.1
2	17.3	60.7
3	24.3	79.2
4	30.9	90.7
5	36.9	96.9
6	42.9	100.1
7	48.2	101.4
8	53.1	101.9
9	57.6	102
10	61.8	102
11	65.7	102
12	69.3	102
13	72.4	102
14	75.4	102
15	78	102
16	80.3	102
18	84.3	
20	87.3	

[0292] The data are compared with the data from Example 14 in Figure 3. An influence of the dissolution medium on the dissolution rate is observed, i.e. the choice of dissolution method is important (not only with respect to pH but also with respect to factors like, e.g., ionic strength, osmotic pressure etc.).

EXAMPLE 16

Investigation of the influence of a pre-treatment in 0.1 N hydrochloric acid on the dissolution rate at pH 7.4

[0293] Dissolution data from coated pellets from Example 4 and Example 8 (batch 2) was determined by dissolution method I (pH 7.4) and method IV (1 hour at a pH corresponding to 0.1 N HCl and then at pH 7.4) and are as follows:

Time (h) in pH 7.4	26029832 (3,0/25) (HCl/7,4) Example 8, batch 2 Dissolution method IV	20029832 (3,0/4,3) (HCl/7,4) Example 4, Dissolution method IV	20029832 (3,0/4,3) Example 8 batch 2 Dissolution method I	26029832 (3,0/25,0) Example 4, Dissolution method I
0	0	0	0	0
0.5			10.1	32.7
1	47.6	16.9	16.9	52.6
2	77.5	29.1	28.5	82.1
3	92.4	39.6	39.7	96.9
4	98.1	48.3	50	101.9
5	100.2	56.9	58.9	102.9
6	100.6	64.8	69.1	103
7	100.6	71.6	76.2	103.2
8	100.7	77	82.2	102.9
9			86.9	102.9
10		85.7	90.5	103.1
11		88.8	93.4	102.9

(continued)

Time (h) in pH 7.4	26029832 (3,0/25) (HCl/7,4) Example 8, batch 2 Dissolution method IV	20029832 (3,0/4,3) (HCl/7,4) Example 4, Dissolution method IV	20029832 (3,0/4,3) Example 8 batch 2 Dissolution method I	26029832 (3,0/25,0) Example 4, Dissolution method I
12		91.3	93.4	
13		93.4	95.2	
14		94.8	97.7	
15		96	97.9	
16		97	98	
17		97.6	98.7	
18		98.3	98.8	
19		98.6	99	

[0294] The dissolution results from Example 16 reveal that a pre-treatment with acid does not have any significantly influence on the rate of release from the delayed release fraction, i.e. the coated pellets fraction.

[0295] In Figure 4 the data are presented and in order to make a proper comparison possible, the release data obtained by dissolution method IV have been displaced by 1 hour corresponding to the time period for treatment in 0.1 N HCl. Thus, in Figure 4, the zero setting for all compositions is when the dissolution medium has a pH of 7.4. The observed differences with respect to the dissolution of lornoxicam from Example 1 and 4, respectively, are not significant and are within the standard deviation observed.

Conclusion with respect to Examples 15 and 16

[0296] The results from Examples 15 and 16 have shown that coated pellets have the same release rate independent on whether a pre-treatment in acid has been included or not whereas a change in the dissolution method (from method I to method V) has a significant influence on the release rate.

EXAMPLE 17

Investigation on the influence of dose on the dissolution rate

[0297] In this Example the dissolution profiles of a dose of 16 mg of lornoxicam are compared to a dose of 8 mg of lornoxicam. Dissolution profiles are obtained according to dissolution method III.

Time (h)	972510 + 24029832 8 mg Example 12 8 mg lornoxicam pr. capsule	972510 + 24029832 Reanalysis of Example 12 (new sample) 8 mg lornoxicam pr. capsule	972510 + 24029832 Reanalysis of Example 12 (new sample) 16 mg lornoxicam pr. capsule
0	0	0	0
1	35.7	36.2	35.3
2	43.2	47	46.3
3	50.0	55.9	55
4	55.8	63.9	61.7
5	60.9	70.6	67.1
6	66.2	77.4	73.1
7	70.7	83	77.1
8	74.4	87.1	81.4
9	78.3	91.3	85.5
10	81.5	94.2	90.5
11	84.8	95.9	91.9
12	87.3	97.8	93.9
13	89.3	98.7	95.7

(continued)

Time (h)	972510 + 24029832 8 mg Example 12 8 mg lornoxicam pr. capsule	972510 + 24029832 Reanalysis of Example 12 (new sample) 8 mg lornoxicam pr. capsule	972510 + 24029832 Reanalysis of Example 12 (new sample) 16 mg lornoxicam pr. capsule
14	91.1	99	96.7
15	92.6	99.9	97.7
16	93.8	99.9	98.1
17	95.0	99.7	99
18	95.9	100.1	99.1
19	96.6		
20	97.2		
21	97.5		
22	97.8		
23	98.0		
24	97.5		

[0298] Data are presented in Figure 5 and the curves show that the dose is without any significant influence on the release rate. In Figure 5 a target profile calculated for lornoxicam has been included and it is seen that the compositions tested have profiles very close to the target profile.

EXAMPLE 18

Investigation on whether a plain granulate quickly releases an NSAID substance

[0299] A granulate containing naproxen was prepared using the ingredients listed in Table 10. The granulate was prepared in order to investigate whether a plain granulate like the one disclosed in EP-A-0 438 249A1 (ELAN Corporation P.L.C.) releases naproxen quickly (as defined herein) when the dissolution testing is done according to dissolution method II (n = 2) described herein. No standards were used and, accordingly, a literature value for E (1%, 1 cm) = 63 was used to calculate the content in the samples. The composition of the granulate corresponds to the one disclosed in Example 1 of EP-A-0 438 249A1 (ELAN Corporation P.L.C.).

Table 10

Ingredients	Amount (g)
Naproxen	232.0
Polyvidone 30	7.2
Isopropanol	65.7

[0300] Naproxen and polyvidone 30 were mixed in a lab scale Kenwood mixer for 3 min. The mixture was granulated by slowly adding the isopropanol over a period of 2 min and the mixing was continued for 1 min. Then the granulate was dried on trays at 50 °C for 12 hours. Thereafter half of the granulate was sieved through a 500 µm sieve and the other half of the granulate was sieved through a 1000 µm sieve. Oversized material was discarded in both cases. The thus obtained two granulates were tested according to dissolution method II described herein.

[0301] Batch No. 26089831: 500 µm sieved granulate in an amount corresponding to a 150 mg tablet. In the following is given the results from the dissolution test.

Time (h)	Release (dissolved naproxen) % w/w
0	0
0.5	15
1	16.1
1.5	16.5
2	17.6

[0302] Batch No. 26089831: 1000 µm sieved granulate in an amount corresponding to a 150 mg tablet. In the following

is given the results from the dissolution test.

Time (h)	Release (dissolved naproxen) % w/w
0	0
0.5	11.4
1	13.4
1.5	14.2
2	15.7

[0303] From the results given above, it is clear that such plain formulations do not release the NSAID substance very fast and, accordingly, such formulations or compositions do not fall under the definition of quick release defined herein (i.e. that at least about 50% of the NSAID substance is released within the first 20 min of the dissolution test).

Claims

1. An oral pharmaceutical modified release multiple-units composition in unit dosage form for administration of a therapeutically and/or prophylactically effective amount of a non-steroidal anti-inflammatory drug substance, an NSAID substance, said unit dosage form comprising at least two NSAID-containing fractions,

   i) a first NSAID-containing fraction of multiple-units for quick release of the NSAID substance, wherein said fraction comprises an antacidsubstance or an alkaline agent and wherein the quick in vitro release is such that, when subjecting the first NSAID-containing fraction to dissolution method II employing 0.07 N HCl as dissolution medium, at least 50% w/w of the NSAID substance is released within the first 20 min of the test; and

   ii) a second NSAID-containing fraction of multiple-units in the form of coated delayed release multiple units, said units coated with a coating that is water-insoluble, but water-diffusible and pH-independent.

2. The composition according to claim 1, wherein the first fraction, when subjected to dissolution method II as defined herein employing 0.07 N HCl as dissolution medium, releases at least 55% w/w such as at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 75% w/w or at least 80% w/w of the total NSAID substance present in the first fraction within the first 20 min of the test.

3. The composition according to any one of claims 1 to 2, wherein the quick release and the extended release are such that the first fraction is released *in vitro* when the *in vitro* release from the second fraction is initiated, corresponding to at least 50% w/w release of the NSAID substance contained in the first fraction at the time when at the most 15% w/w, such as at the most 10% w/w or at the most 5% w/w of the NSAID substance contained in the second fraction is released as determined by the dissolution method III defined herein.

4. The composition according to any one of claims 1 to 3, wherein the first fraction is in the form of un-coated units.

5. The composition according to claim 4, wherein the NSAID substance contained in the first fraction has a pK_a value between from 3.0 to 5.5.

6. The composition according to any one of claims 3 to 4, wherein the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at the most 0.5% w/v such as at the most 0.1% w/v, at the most 0.05% w/v, at the most 0.03% w/v, at the most 0.01% w/w, at the most 0.007% w/v, at the most 0.005% w/v, at the most 0.003% w/v, at the most 0.002% w/v or at the most 0.001% w/v.

7. The composition according to any one of claims 1 to 3, wherein the first fraction is in the form of coated units.

8. The composition according to claim 7, wherein the NSAID substance contained in the first fraction has a pK_a value of at least 5.0, such as at least 5.5.

9. The composition according to any one of claims 7 or 8, wherein the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at least 0.1% w/v such as at least 0.5% w/v or at least 1% w/v.

10. The composition according to any one of the preceding claims for the administration of a therapeutically and/or prophylactically effective amount of an NSAID substance to obtain both a relatively fast onset of the therapeutic effect and the maintenance of therapeutically active plasma concentration for a relatively long period of time, a unit dosage of the composition comprising at least two fractions as follows:

    a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically and/or prophylactically active plasma concentration within a relatively short period of time, and

    a second fraction of coated modified release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically and/or prophylactically active plasma concentration in order to enable dosing once or twice daily,

    the formulation of the first and the second fractions, with respect to release therefrom and with respect to the ratio between the first and the second fraction in the unit dosage, being adapted so as to obtain:

        a relative quick *in vitro* release of the NSAID substance from the first fraction of quick release multiple-units, as determined by the dissolution method II as defined herein,

        an extended *in vitro* release of the NSAID substance from the second fraction of extended release multiple-units relative to the *in vitro* release of the first fraction of the NSAID substance, as determined by the dissolution method III as defined herein,

        the quick release and the extended *in vitro* release being adapted so that the first fraction is released when the release from the second fraction is initiated corresponding to at least 50% w/w release of the NSAID substance contained in the first fraction at the time when at least 15% w/w such as at least 10% w/w or at least 5% w/w of the NSAID substance contained in the second fraction is released as determined by the dissolution method III defined herein.

11. The composition according to any one of the preceding claims, wherein the NSAID substance is selected from the group consisting of lornoxicam, diclofenac, nimesulide, ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen, ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acemetacin, morniflumate, meloxicam, flurbiprofen, tiaprofenic acid, proglumetacin, mefenamic acid, fenbufen, etodolac, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen, and pharmaceutically acceptable salts, complexes and/or prodrugs thereof and mixtures thereof.

12. The composition according to any one of the preceding claims, wherein the NSAID substance in the first fraction is the same as the NSAID substance contained in the second fraction.

13. The composition according to any one of claims 1 to 11, wherein the NSAID substance in the first fraction is different from the NSAID substance contained in the second fraction.

14. The composition according to any one of the preceding claims, wherein the NSAID substance in the first fraction is lornoxicam.

15. The composition according to any one of the preceding claims, wherein the NSAID substance in the second fraction is lornoxicam.

16. The composition according to any one of the preceding claims comprising a further active drug substance.

17. The composition according to any one of the preceding claims, wherein a further active drug substance is included in at least one of the first and second fraction.

18. The composition according to any one of claims 16 or 17, wherein the further active drug substance is selected from the group consisting of an antidepressant, an opioid, a prostaglandine analog , a glucocorticosteroid, a cytostaticum , a H_2 receptor antagonist , a proton pump inhibitor and/or an antacidum.

19. The composition according to any one of claims 16 or 17, wherein the further active drug substance is selected

from the group consisting of paracetamol, penicillamine, sulfasalazine and auranorfin.

20. The composition according to any one of the preceding claims, wherein the NSAID substance is lornoxicam.

21. The composition according to any one of the preceding claims, wherein the quick release multiple-units of the first fraction have a mean particle size of at the most 250 μm such as, at the most 240 μm, at the most 230 μm, at the most 220 μm, at the most abut 210 μm, at the most 200 μm, at the most 190 μm, at the most 180 μm, at the most 175 μm, at the most 150 μm, at the most 125 μm, at the most 100 μm, at the most 90 μm or at the most 80 μm.

22. The composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the first fraction of quick release multiple-units provides within 1 hour a release of said NSAID substance as determined by the dissolution method II defined herein of at least 50% w/w, such as at least 60% w/w, at least 70% w/w, at at least 80% w/w, at least 85% w/w at least 90% w/w or at least 95% w/w of the NSAID substance.

23. The composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of extended release multiple-units provides within 1 hour a release as determined by the dissolution method III defined herein in the range of 0%-30% w/w, such as in the range of 0%-20% w/w, in the range of 0%-10% w/w, such as at the most 5% w/w of the NSAID substance.

24. The composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of extended release multiple-units provides within 3 hours a release as determined by the dissolution method III defined herein in the range of 10%-70% w/w, such as in the range of 10%-60% w/w, in the range of 12%-50% w/w, in the range of 14%-45% w/w, in the range of 15%-30% w/w, in the range of 15%-20% w/w such as 17% w/w of the NSAID substance.

25. The composition according to any one of the preceding claims, wherein the in *vitro* dissolution characteristics of the second fraction of extended release multiple-units provides within 6 hours a release as determined by the dissolution method III defined herein in the range of 35%-95% w/w, such as in the range of 50%-90% w/w, in the range of 50%-80% w/w, in the range of 50%-75% w/w, in the range of 50%-60% w/w, in the range of 53%-59% w/w such as 56% w/w of the NSAID substance.

26. The composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of modified release multiple-units provides within 9 hours a release of said NSAID substance as determined by the dissolution method III defined herein in the range of 50%-100% w/w, such asin the range of 60%-98% w/w, in the range of 65%-95% w/w, in the range of 70%-90% w/w, in the range of 70%-80% w/w such as 76% w/w of the NSAID substance.

27. The composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the first and second fractions are adapted so that the NSAID substance from the first fraction is released when the release of the said NSAID substance from the second fraction is initiated corresponding to at least 50% w/w of the first fraction at the time at the most 15% w/w such as at the most 10% w/w or at the most 5% w/w of the NSAID substance in the second fraction is released, as determined by the dissolution method III defined herein.

28. The composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the first and second fractions are adapted so that the NSAID substance from the first fraction is released when the release of the said NSAID substance from the second fraction is initiated corresponding to at least 70% w/w release of the first fraction at the time at the most 20% w/w of the NSAID substance such as at the most 15% or at the most 10% w/w of the second fraction is released as determined by the dissolution method III as defined herein.

29. The composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 1 hour a release of the NSAID substance from the composition in the range of 5-50% w/w, such as in the range of 5-45% w/w, in the range of 15-40% w/w, in the range of 20-35% w/w such as 29% w/w, as determined by the dissolution method III as defined herein.

30. The composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 3 hours a release of the NSAID substance from the composition as determined by the dissolution method III as defined herein in the range of 20-80% w/w, such as in the range of 25-70% w/w, in the range of 30-60% w/w, in the range of 35-55% w/w such as 42% w/w.

31. The composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 6 hours a release of the NSAID substance as determined by the dissolution method III defined herein in the range of 40-98% w/w,such as in the range of 50-95% w/w, in the range of 60-90% w/w, in the range of 60-85% w/w, most preferred in the range of 60-83% w/w such as 69% w/w.

32. The composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 9 hours a release of the NSAID substance as determined by the dissolution method III as defined herein in the range of 50-100% w/w, such as in the range of 60-99% w/w, in the range of 70-98% w/w, in the range of 70-97% w/w, in the range of 75-96% w/w, in the range of 80-96% w/w, 80-85% w/w such as 83% w/w.

33. The composition according to any one of the preceding claims, wherein the percentage of NSAID substance in the first fraction is in the range of 5%-50% w/w such as in the range of 10%-45% w/w, in the range of 15%-45% w/w, in the range of 20%-40% w/w, in the range of 25%-40% w/w, in the range of 25%-35% w/w such as 30% w/w in relation to the total amount of NSAID substance in the composition.

34. The composition according to any one of the preceding claims, wherein the percentage of NSAID substance in the second fraction is in the range of 30%-99% w/w such as in the range of 40%-98% w/w, in the range of 45%-95% w/w, in the range of 50%-95% w/w, in the range of 55%-85% w/w, in the range of 60%-80% w/w, in the range of 60%-75% w/w, in the range of abut 65%-75% w/w such as 70% w/w in relation to the total amount of NSAID substance in the composition.

35. The composition according to any one of the preceding claims, wherein the multiple-units of the second fraction are coated cross-sectionally substantially homogeneous pellets.

36. The composition according to any one of the preceding claims, wherein the multiple-units of the first fraction are cross-sectionally substantially homogeneous pellets.

37. The composition according to any one of claims 6 to 36, wherein the first fraction is coated units and the coating is a water-insoluble, but water-diffusible and pH-independent coating.

38. The composition according to any one of the preceding claims, wherein a unit dosage of the composition comprises from 1 to 32 mg of the NSAID substance.

39. The composition according to any one of the preceding claims, wherein a unit dosage comprises from 1 mg to 1.6 g such as from 1 mg to 1.2 g of the NSAID substance.

40. The composition according to any one of the preceding claims, wherein a unit dosage comprises from 50 mg to 1.1 g of the NSAID substance.

41. The composition according to any one of the preceding claims, wherein a unit dosage comprises from 100 mg to 1.0 g of the NSAID substance.

42. The composition according to any one of claims the preceding claims, wherein a unit dosage comprises from 200 mg to 900 mg of the NSAID substance.

43. The composition according to any one of claims the preceding claims, wherein a unit dosage comprises from 300 mg to 800 mg of the NSAID substance.

44. The composition according to any one of the preceding claims, wherein the unit dosage of the composition is in the form of a capsule, tablet or sachet.

45. The composition according to any one of the preceding claims, wherein the NSAID substance is lornoxicam and the unit dosage of the composition contains 4, 8, 12, 16, 20, 24, 28, 32 or 36 mg of lornoxicam.

46. The composition according to any one of preceding claims, comprising at least 100 multiple units.

47. The composition according to any one of preceding claims, wherein the first fraction of multiple units is in the form

of granules.

48. A process for the preparation of a unit dosage form of an oral pharmaceutical modified release composition comprising the steps of:

i) providing
a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance, wherein said fraction comprises an antacidsubstance or an alkaline agent and wherein the quick in vitro release being such that when subjecting the first NSAID-containing fraction to dissolution method II employing 0.07 N HCl as dissolution medium at least 50% w/w of the NSAID substance is released within the first 20 min of the test;

ii) providing a second fraction of coated extended release multiple-units for extended release *in vivo* of an NSAID substance, wherein said coated units comprise a coating that is water-insoluble, but water-diffusible and pH-independent;

iii) combining and formulating the first and the second fractions with respect to release therefrom and with respect to the ratio between the first and the second fraction such that the first fraction is released when the in vitro release from the second fraction is initiated corresponding to at least 50% w/w release of the NSAID substance contained in the first fraction at the time when at the most 15% w/w such as at the most 10% w/w or at the most 5% w/w of the NSAID substance contained in the second fraction is released as determined by the dissolution method III as defined herein; and

iv) incorporating into the unit dosage form at least said two fractions i) and ii).

49. A process according to claim 48, wherein the composition is as defined in any one of claims 1 to 47.

50. Use of a non-steroidal anti-inflammatory drug substance for the preparation of a medicament for the treatment of inflammation and/or pain,
wherein said medicament comprises is a modified release multiple-units composition in unit dosage form, said unit dosage form comprising at least two NSAID-containing fractions,

i) a first NSAID-containing fraction of multiple-units for quick release of the NSAID substance, wherein said fraction comprises an antacid substance or an alkaline agent, and wherein the quick in vitro release is such that, when subjecting the first NSAID-containing fraction to dissolution method II employing 0.07 N HCl as dissolution medium, at least 50% w/w of the NSAID substance is released within the first 20 min of the test; and

ii) a second NSAID-containing fraction of multiple-units in the form of coated delayed release multiple units,

said units coated with a coating water-insoluble, but water-diffusible and pH-independent.

51. The use according to claim 50, wherein the medicament comprises a composition as defined in any one of claims 1 to 47.

Patentansprüche

1. Orale, pharmazeutische Multiple-units-Zusammensetzung mit modifizierter Freisetzung in Dosierungseinheitsform zur Verabreichung einer therapeutisch und/oder prophylaktisch wirksamen Menge einer nicht-steroidalen antiinflammatorischen Arzneimittelsubstanz, einer NSAID-Substanz, wobei die Dosierungseinheitsform mindestens zwei NSAID-enthaltende Fraktionen umfasst:

i) eine erste NSAID-enthaltende Fraktion aus Multiple-units zur schnellen Freisetzung der NSAID-Substanz, wobei die Fraktion ein Antazidum oder ein alkalisches Mittel umfasst und wobei die schnelle *in-vitro*-Freisetzung so ist, dass, wenn die erste NSAID-enthaltende Fraktion einem Auflösungsverfahren II, das 0,07 N HCl als Auflösungsmedium verwendet, unterworfen wird, mindestens 50 Gew.-% der NSAID-Substanz in den ersten 20 min des Tests freigesetzt werden; und

ii) eine zweite NSAID-enthaltende Fraktion aus Multiple-units in Form überzogener Multiple-units mit verzö-

gerter Freisetzung,

wobei die Units mit einem Überzug überzogen sind, der in Wasser unlöslich ist, aber in Wasser diffusionsfähig und pH-unabhängig ist.

2. Zusammensetzung nach Anspruch 1, wobei die erste Fraktion, wenn sie einem Auflösungsverfahren II, wie es hier definiert wird, das 0,07 N HCl als Auflösungsmedium verwendet, unterworfen wird, mindestens 55 Gew.-%, z.B. mindestens 60 Gew.-%, mindestens 65 Gew.-%, mindestens 70 Gew.-%, mindestens 75 Gew.-% oder mindestens 80 Gew.-% der gesamten NSAID-Substanz, die in der ersten Fraktion vorliegt, innerhalb der ersten 20 min des Tests freisetzt.

3. Zusammensetzung nach Anspruch 1 oder Anspruch 2, wobei die schnelle Freisetzung und die verlängerte Freisetzung so sind, dass die erste Fraktion *in vitro* freigesetzt ist, wenn die *in-vitro*-Freisetzung aus der zweiten Fraktion initiiert wird, was einer Freisetzung von mindestens 50 Gew.-% der NSAID-Substanz, die in der ersten Fraktion enthalten ist, zu der Zeit entspricht, wenn höchstens 15 Gew.-%, z.B. höchstens 10 Gew.-% oder höchstens 5 Gew.-% der NSAID-Substanz, die in der zweiten Fraktion enthalten ist, freigesetzt ist, was nach dem hierin definierten Auflösungsverfahren III bestimmt wird.

4. Zusammensetzung nach einem der Ansprüche 1 bis 3, wobei die erste Fraktion in Form von nicht-überzogenen Units vorliegt.

5. Zusammensetzung nach Anspruch 4, wobei die NSAID-Substanz, die in der ersten Fraktion enthalten ist, einen pK_a-Wert zwischen 3,0 und 5,5 hat.

6. Zusammensetzung nach Anspruch 3 oder 4, wobei die NSAID-Substanz bei Raumtemperatur eine Löslichkeit in 0,1 N Salzsäure von höchstens 0,5% Gew./Vol., z.B. höchstens 0,1% Gew./Vol., höchstens 0,05% Gew./Vol., höchstens 0,03% Gew./Vol., höchstens 0,01% Gew./Gew., höchstens 0,007% Gew./Vol., höchstens 0,005% Gew./Vol., höchstens 0,003% Gew./Vol., höchstens 0,002% Gew./Vol. oder höchstens 0,001% Gew./Vol. hat.

7. Zusammensetzung nach einem der Ansprüche 1 bis 3, wobei die erste Fraktion in Form überzogener Units ist.

8. Zusammensetzung nach Anspruch 7, wobei die NSAID-Substanz, die in der ersten Fraktion enthalten ist, einen pK_a-Wert von mindestens 5,0, z.B. mindestens 5,5, hat.

9. Zusammensetzung nach Anspruch 7 oder Anspruch 8, wobei die NSAID-Substanz bei Raumtemperatur eine Löslichkeit in 0,1 N Salzsäure von mindestens 0,1% Gew./Vol., z.B. mindestens 0,5% Gew./Vol. oder mindestens 1% Gew./Vol. hat.

10. Zusammensetzung nach einem der vorangehenden Ansprüche zur Verabreichung einer therapeutisch und/oder prophylaktisch wirksamen Menge einer NSAID-Substanz um sowohl ein relativ schnelles Einsetzen der therapeutischen Wirkung als auch die Aufrechterhaltung einer therapeutisch aktiven Plasmakonzentration über einen relativ langen Zeitraum zu erreichen, wobei die Dosierungseinheit der Zusammensetzung mindestens zwei Fraktionen wie folgt umfasst:

eine erste Fraktion aus Multiple-units zur schnellen Freisetzung für eine relativ schnelle *in-vivo*-Freisetzung einer NSAID-Substanz um eine therapeutisch und/oder prophylaktisch aktive Plasmakonzentration innerhalb eines relativ kurzen Zeitraums zu erhalten, und

eine zweite Fraktion aus überzogenen Multiple-units mit modifizierter Freisetzung für eine verlängerte *in-vivo*-Freisetzung einer NSAID-Substanz um eine therapeutisch und/oder prophylaktisch aktive Plasmakonzentration aufrechtzuerhalten um so einmal oder zweimal täglich eine Dosierung zu ermöglichen,

wobei die Formulierung der ersten Fraktion und der zweiten Fraktion bezüglich ihrer Freisetzung und bezüglich des Verhältnisses zwischen der ersten Fraktion und der zweiten Fraktion in der Dosierungseinheit so angepasst sind, dass erreicht wird:

eine relativ schnelle *in-vitro*-Freisetzung der NSAID-Substanz aus der ersten Fraktion aus Multiple-units mit schneller Freisetzung, wie sie durch das hierin definierte Auflösungsverfahren II definiert wird,

eine verlängerte *in-vitro*-Freisetzung der NSAID-Substanz aus der zweiten Fraktion aus Multiple-units mit verlängerter Freisetzung bezüglich der *in-vitro*-Freisetzung der ersten Fraktion der NSAID-Substanz, wie sie durch das hierin definierte Auflösungsverfahren III bestimmt wird,

wobei die schnelle Freisetzung und die verlängerte in-vitro-Freisetzung so angepasst sind, dass die erste Fraktion freigesetzt ist, wenn die Freisetzung aus der zweiten Fraktion initiiert wird, was einer mindestens 50 Gew.-%igen Freisetzung der NSAID-Substanz, die in der ersten Fraktion enthalten ist, zu der Zeit entspricht, wenn mindestens 15 Gew.-%, z.B. mindestens 10 Gew.-% oder mindestens 5 Gew.-% der NSAID-Substanz, die in der zweiten Fraktion enthalten ist, freigesetzt sind, wie es durch das hierin definierte Auflösungsverfahren III bestimmt wird.

11. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die NSAID-Substanz aus der Gruppe bestehend aus Lornoxicam, Diclofenac, Nimesulid, Ibuprofen, Piroxicam, Piroxicam (Betacyclodextrin), Naproxen, Ketoprofen, Tenoxicam, Aceclofenac, Indometacin, Nabumeton, Acemetacin, Morniflumat, Meloxicam, Flurbiprofen, Tiaprofensäure, Proglumetacin, Mefenaminsäure, Fenbufen, Etodolac, Tolfenaminsäure, Sulindac, Phenylbutazon, Fenoprofen, Tolmetin, Acetylsalicylsäure, Dexibuprofen und pharmazeutisch annehmbaren Salzen, Komplexen und/oder Prodrugs davon und Gemischen davon ausgewählt ist.

12. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die NSAID-Substanz in der ersten Fraktion dieselbe ist wie die NSAID-Substanz, die in der zweiten Fraktion enthalten ist.

13. Zusammensetzung nach einem der Ansprüche 1 bis 11, wobei die NSAID-Substanz in der ersten Fraktion eine andere ist als die NSAID-Substanz, die in der zweiten Fraktion enthalten ist.

14. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die NSAID-Substanz in der ersten Fraktion Lornoxicam ist.

15. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die NSAID-Substanz in der zweiten Fraktion Lornoxicam ist.

16. Zusammensetzung nach einem der vorangehenden Ansprüche, die eine weitere aktive Arzneimittelsubstanz umfasst.

17. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei eine weitere aktive Arzneimittelsubstanz in mindestens einer der ersten und zweiten Fraktion enthalten ist.

18. Zusammensetzung nach Anspruch 16 oder Anspruch 17, wobei die weitere aktive Arzneimittelsubstanz aus der Gruppe bestehend aus einem Antidepressivum, einem Opioid, einem Prostaglandinanalogon, einem Glucocorticosteroid, einem Cytostatikum, einem H_2-Rezeptorantagonisten, einem Protonenpumpeninhibitor und/oder einem Antazidum ausgewählt ist.

19. Zusammensetzung nach Anspruch 16 oder 17, wobei die weitere aktive Arzneimittelsubstanz aus der Gruppe bestehend aus Paracetamol, Penicillamin, Sulfasalazin und Auranorfin ausgewählt ist.

20. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die NSAID-Substanz Lornoxicam ist.

21. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die Multiple-units mit schneller Freisetzung aus der ersten Fraktion eine mittlere Partikelgröße von höchstens 250 µm, z.B. höchstens 240 µm, höchstens 230 µm, höchstens 220 µm, höchstens 210 µm, höchstens 200 µm, höchstens 190 µm, höchstens 180 µm, höchstens 175 µm, höchstens 150 µm, höchstens 125 µm, höchstens 100 µm, höchstens 90 µm oder höchstens 80 µm haben.

22. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die *in-vitro*-Auflösungscharakteristika der ersten Fraktion aus Multiple-units mit schneller Freisetzung innerhalb 1 Stunde eine Freisetzung der NSAID-Substanz, wie sie durch das hierin definierte Auflösungsverfahren II bestimmt wird, von mindestens 50 Gew.-%, z.B. mindestens 60 Gew.-%, mindestens 70 Gew.-%, mindestens 80 Gew.-%, mindestens 85 Gew.-%, mindestens 90 Gew.-% oder mindestens 95 Gew.-% der NSAID-Substanz liefern.

23. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die *in-vitro*-Auflösungscharakteristika der zweiten Fraktion aus Multiple-units mit verlängerter Freisetzung innerhalb 1 Stunde eine Freisetzung der

NSAID-Substanz, wie sie durch das hierin definierte Auflösungsverfahren III bestimmt wird, im Bereich von 0 Gew.-% bis 30 Gew.-%, z.B. im Bereich von 0 Gew.-% bis 20 Gew.-%, im Bereich von 0 Gew.-% bis 10 Gew.-%, z.B. höchstens 5 Gew.-%, liefern.

24. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die *in-vitro*-Auflösungscharakteristika der zweiten Fraktion aus Multiple-units mit verlängerter Freisetzung innerhalb von 3 Stunden eine Freisetzung der NSAID-Substanz, wie sie durch das hierin definierte Auflösungsverfahren III definiert wird, im Bereich von 10 bis 70 Gew.-%, z.B. im Bereich von 10 Gew.-% bis 60 Gew.-%, im Bereich von 12 Gew.-% bis 50 Gew.-%, im Bereich von 14 Gew.-% bis 45 Gew.-%, im Bereich von 15 Gew.-% bis 30 Gew.-%, im Bereich von 15 Gew.-% bis 20 Gew.-%, z.B. 17 Gew.-%, bereitstellen.

25. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die *in-vitro*-Auflösungscharakteristika der zweiten Fraktion aus Multiple-units mit verlängerter Freisetzung innerhalb von 6 Stunden eine Freisetzung der NSAID-Substanz, wie sie durch das hierin definierte Auflösungsverfahren III definiert ist, im Bereich von 35 bis 95 Gew.-%, z.B. im Bereich von 50 Gew.-% bis 90 Gew.-%, im Bereich von 50 Gew.-% bis 80 Gew.-%, im Bereich von 50 Gew.-% bis 75 Gew.-%, im Bereich von 50 Gew.-% bis 60 Gew.-%, im Bereich von 53 Gew.-% bis 59 Gew.-%, z.B. 56 Gew.-%, bereitstellen.

26. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die *in-vitro*-Auflösungscharakteristika der zweiten Fraktion aus Multiple-units mit modifizierter Freisetzung innerhalb von 9 Stunden eine Freisetzung der NSAID-Substanz, wie sie durch das hierin definierte Auflösungsverfahren III bestimmt wird, im Bereich von 50 Gew.-% bis 100 Gew.-%, z.B. im Bereich von 60 Gew.-% bis 98 Gew.-%, im Bereich von 65 Gew.-% bis 95 Gew.-%, im Bereich von 70 Gew.-% bis 90 Gew.-%, im Bereich von 70 Gew.-% bis 80 Gew.-%, z.B. 76 Gew.-% der NSAID-Substanz, bereitstellen.

27. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die *in-vitro*-Auflösungscharakteristika der ersten Fraktion und der zweiten Fraktion so angepasst sind, dass die NSAID-Substanz aus der ersten Fraktion freigesetzt ist, wenn die Freisetzung der NSAID-Substanz aus der zweiten Fraktion initiiert wird, was einer Freisetzung von mindestens 50 Gew.-% der ersten Fraktion zu der Zeit entspricht, zu der höchstens 15 Gew.-%, z.B. höchstens 10 Gew.-% oder höchstens 5 Gew.-% der NSAID-Substanz in der zweiten Fraktion freigesetzt sind, was durch das hierin definierte Auflösungsverfahren III bestimmt wird.

28. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die *in-vitro*-Auflösungscharakteristika der ersten Fraktion und der zweiten Fraktion so angepasst sind, dass die NSAID-Substanz aus der ersten Fraktion freigesetzt ist, wenn die Freisetzung der NSAID-Substanz aus der zweiten Fraktion initiiert wird, was einer Freisetzung von mindestens 70 Gew.-% der ersten Fraktion zu der Zeit entspricht, zu der höchstens 20 Gew.-% der NSAID-Substanz, z.B. höchstens 15 Gew.-% oder höchstens 10 Gew.-% der zweiten Fraktion freigesetzt sind, was durch das hierin definierte Auflösungsverfahren III bestimmt wird.

29. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die *in-vitro*-Auflösungscharakteristika der Zusammensetzung innerhalb 1 Stunde eine Freisetzung der NSAID-Substanz aus der Zusammensetzung im Bereich von 5 bis 50 Gew.-%, z.B. im Bereich von 5 bis 45 Gew.-%, im Bereich von 15 bis 40 Gew.-%, im Bereich von 20 bis 30 Gew.-%, z.B. 29 Gew.-%, wie sie durch das hierin definierte Auflösungsverfahren III bestimmt wird, bereitstellen.

30. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die *in-vitro*-Auflösungscharakteristika der Zusammensetzung innerhalb von 3 Stunden eine Freisetzung der NSAID-Substanz aus der Zusammensetzung, wie sie durch das hierin definierte Auflösungsverfahren III bestimmt wird, im Bereich von 20 Gew.-% bis 80 Gew.-%, z.B. im Bereich von 25 Gew.-% bis 70 Gew.-%, im Bereich von 30 Gew.-% bis 60 Gew.-%, im Bereich von 35 Gew.-% bis 55 Gew.-%, z.B. 42 Gew.-%, liefern.

31. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die *in-vitro*-Auflösungscharakteristika der Zusammensetzung innerhalb von 6 Stunden eine Freisetzung der NSAID-Substanz, wie sie durch das hierin definierte Auflösungsverfahren III bestimmt wird, im Bereich von 40 Gew.-% bis 98 Gew.-%, z.B. im Bereich von 50 Gew.-% bis 95 Gew.-%, im Bereich von 60 Gew.-% bis 90 Gew.-%, im Bereich von 60 Gew.-% bis 85 Gew.-%, am bevorzugtesten im Bereich von 60 Gew.-% bis 83 Gew.-%, z.B. 69 Gew.-%, bereitstellen.

32. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die *in-vitro*-Auflösungscharakteristika der

Zusammensetzung innerhalb von 9 Stunden eine Freisetzung der NSAID-Substanz, wie sie durch das hierin definierte Auflösungsverfahren III bestimmt wird, im Bereich von 50 bis 100 Gew.-%, z.B. im Bereich von 60 bis 99 Gew.-%, im Bereich von 70 bis 98 Gew.-%, im Bereich von 70 bis 97 Gew.-%, im Bereich von 75 bis 96 Gew.-%, im Bereich von 80 bis 96 Gew.-%, 80 bis 85 Gew.-%, z.B. 83 Gew.-%, bereitstellen.

33. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei der prozentuale Anteil der NSAID-Substanz in der ersten Fraktion im Bereich von 5 bis 50 Gew.-%, z.B. im Bereich von 10 bis 45 Gew.-%, im Bereich von 15 bis 45 Gew.-%, im Bereich von 20 bis 40 Gew.-%, im Bereich von 25 bis 40 Gew.-%, im Bereich von 25 bis 35 Gew.-%, z.B. 30 Gew.-%, bezogen auf die Gesamtmenge der NSAID-Substanz in der Zusammensetzung, ist.

34. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei der prozentuale Anteil der NSAID-Substanz in der zweiten Fraktion im Bereich von 30 bis 99 Gew.-%, z.B. im Bereich von 40 bis 98 Gew.-%, im Bereich von 45 bis 95 Gew.-%, im Bereich von 50 bis 95 Gew.-%, im Bereich von 55 bis 85 Gew.-%, im Bereich von 60 bis 80 Gew.-%, im Bereich von 60 bis 75 Gew.-%, im Bereich von 65 bis 75 Gew.-%, z.B. 70 Gew.-%, bezogen auf die Gesamtmenge der NSAID-Substanz in der Zusammensetzung, ist.

35. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die Multiple-units der zweiten Fraktion überzogene, im Querschnitt im Wesentlichen homogene Pellets sind.

36. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die Multiple-units der ersten Fraktion im Querschnitt im Wesentlichen homogene Pellets sind.

37. Zusammensetzung nach einem der Ansprüche 6 bis 36,
wobei die erste Fraktion überzogene Units sind und der Überzug ein wasserunlöslicher, aber Wasser-diffusionsfähiger und pH-unabhängiger Überzug ist.

38. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei eine Dosierungseinheit der Zusammensetzung 1 bis 32 mg der NSAID-Substanz umfasst.

39. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei eine Dosierungseinheit 1 mg bis 1,6 g, z. B. 1 mg bis 1,2 g, der NSAID-Substanz umfasst.

40. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei eine Dosierungseinheit 50 mg bis 1,1 g der NSAID-Substanz umfasst.

41. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei eine Dosierungseinheit 100 mg bis 1,0 g der NSAID-Substanz umfasst.

42. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei eine Dosierungseinheit 200 mg bis 900 mg der NSAID-Substanz umfasst.

43. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei eine Dosierungseinheit 300 mg bis 800 mg der NSAID-Substanz umfasst.

44. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die Dosierungseinheit der Zusammensetzung in Form einer Kapsel, Tablette oder eines Briefchens vorliegt.

45. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die NSAID-Substanz Lornoxicam ist und die Dosierungseinheit der Zusammensetzung 4, 8, 12, 16, 20, 24, 28, 32 oder 36 mg Lornoxicam enthält.

46. Zusammensetzung nach einem der vorangehenden Ansprüche, die mindestens 100 Multiple-units umfasst.

47. Zusammensetzung nach einem der vorangehenden Ansprüche, wobei die erste Fraktion aus Multiple-units in Form von Granulat vorliegt.

48. Verfahren zur Herstellung einer Dosierungseinheitsform einer oralen pharmazeutischen Zusammensetzung mit modifizierter Freisetzung, umfassend die Stufen:

i) Bereitstellen einer ersten Fraktion aus Multiple-units mit schneller Freisetzung zur relativ schnellen *in-vivo*-Freisetzung einer NSAID-Substanz, wobei die Fraktion ein Antazidum oder ein alkalisches Mittel umfasst und wobei die schnelle *in-vitro*-Freisetzung so ist, dass, wenn die erste NSAID-enthaltende Fraktion einem Auflösungsverfahren II, das 0,07 N HCl als Auflösungsmedium verwendet, unterworfen wird, mindestens 50 Gew.-% der NSAID-Substanz in den ersten 20 min des Tests freigesetzt werden;

ii) Bereitstellen einer zweiten Fraktion überzogener Multiple-units mit verlängerter Freisetzung für eine verlängerte *in-vivo*-Freisetzung einer NSAID-Substanz, wobei die überzogenen Units einen Überzug umfassen, der in Wasser unlöslich, aber in Wasser diffusionsfähig und pH-unabhängig ist;

iii) Kombinieren und Formulieren der ersten Fraktion und der zweiten Fraktion bezüglich ihrer Freisetzung und bezüglich des Verhältnisses zwischen der ersten und der zweiten Fraktion, so dass die erste Fraktion freigesetzt wird, wenn die *in-vitro*-Freisetzung der zweiten Fraktion initiiert wird, was einer Freisetzung von mindestens 50 Gew.-% der NSAID-Substanz, die in der ersten Fraktion enthalten ist, zu der Zeit entspricht, bei der höchstens 15 Gew.-%, z.B. höchstens 10 Gew.-% oder höchstens 5 Gew.-% der NSAID-Substanz, die in der zweiten Fraktion enthalten ist, freigesetzt sind, wie dies durch das hierin definierte Auflösungsverfahren III bestimmt wird; und

iv) Einarbeiten in die Einheitsdosierungsform mindestens zwei Fraktionen i) und ii).

49. Verfahren nach Anspruch 48, wobei die Zusammensetzung so ist, wie sie in einem der Ansprüche 1 bis 47 definiert ist.

50. Verwendung einer nicht-steroidalen antiinflammatorischen Arzneimittelsubstanz zur Herstellung eines Medikaments zur Behandlung von Entzündungen und/oder Schmerzen,
wobei das Medikament eine Multiple-units-Zusammensetzung mit modifizierter Freisetzung in Einheitsdosierungsform umfasst, wobei die Einheitsdosierungsform mindestens zwei NSAID-enthaltende Fraktionen umfasst:

i) eine erste NSAID-enthaltende Fraktion aus Multiple-units zur schnellen Freisetzung der NSAID-Substanz, wobei die Fraktion ein Antazidum oder ein alkalisches Mittel umfasst und wobei die schnelle *in-vitro*-Freisetzung so ist, dass, wenn die erste NSAID-enthaltende Fraktion einem Auflösungsverfahren II, das 0,07 N HCl als Auflösungsmedium verwendet, unterworfen wird, mindestens 50 Gew.-% der NSAID-Substanz in den ersten 20 min des Tests freigesetzt werden; und

ii) eine zweite NSAID-enthaltende Fraktion aus Multiple-units in Form von überzogenen Multiple-units mit verzögerter Freisetzung,

wobei die units mit einem Überzug überzogen sind, der wasserunlöslich ist, aber in Wasser diffusionsfähig und pH-unabhängig ist.

51. Verwendung nach Anspruch 50, wobei das Medikament eine Zusammensetzung umfasst, wie sie in einem der Ansprüche 1 bis 47 definiert ist.

Revendications

1. Composition pharmaceutique orale contenant des unités multiples à libération modifiée sous forme posologique unitaire destinée à l'administration d'une quantité efficace du point de vue thérapeutique et/ou prophylactique d'une substance médicamenteuse anti-inflammatoire non-stéroïdienne, une substance NSAID, ladite forme posologique unitaire comprenant au moins deux fractions contenant une NSAID,

i) une première fraction contenant une substance NSAID d'unités multiples pour une libération rapide de la substance NSAID, dans laquelle ladite fraction comprend un antiacide ou un agent alcalin et dans laquelle la libération rapide *in vitro* est telle que lorsque l'on soumet la première fraction contenant une NSAID à la méthode de dissolution II utilisant du HCl 0,07 N comme milieu de dissolution, au moins 50 % p/p de la substance NSAID sont libérés au cours des 20 premières minutes du test ; et
ii) une seconde fraction contenant une substance NSAID d'unités multiples sous la forme d'unités multiples enrobées à libération retardée,

lesdites unités enrobées d'un enrobage qui n'est pas hydrosoluble, mais qui peut diffuser dans l'eau et qui est indépendant du pH.

2. Composition selon la revendication 1, dans laquelle la première fraction, lorsqu'elle est soumise à la méthode de dissolution II telle que définie ici utilisant du HCl 0,07 N comme milieu de dissolution, libère au moins 55 % p/p, comme au moins 60 % p/p, au moins 65 % p/p, au moins 70 % p/p, au moins 75 % p/p ou au moins 80 % p/p de la substance NSAID totale présente dans la première fraction au cours des 20 premières minutes du test.

3. Composition selon l'une quelconque des revendications 1 à 2, dans laquelle la libération rapide et la libération prolongée sont telles que la première fraction est libérée *in vitro* lorsque la libération *in vitro* de la seconde fraction est commencée, ce qui correspond à au moins à une libération de 50 % p/p de la substance NSAID contenue dans la première fraction au moment où sont libérés au plus 15 % p/p, tel que au plus 10 % p/p ou au plus 5 % p/p de la substance NSAID contenue dans la seconde fraction comme cela est déterminé par la méthode de dissolution II définie ici.

4. Composition selon l'une quelconque des revendications 1 à 3, dans laquelle la première fraction se présente sous forme d'unités non enrobées.

5. Composition selon la revendication 4, dans laquelle la substance NSAID contenue dans la première fraction a une valeur pK_a comprise entre 3,0 et 5,5.

6. Composition selon l'une quelconque des revendications 3 et 4, dans laquelle la substance NSAID a une solubilité dans de l'acide chlorhydrique 0,1 N à température ambiante d'au plus 0,5 % p/v, par exemple d'au plus 0,1 % p/v, d'au plus 0,05 % p/v, d'au plus 0,03 % p/v, d'au plus 0,01 % p/v, d'au plus 0,007 % p/v, d'au plus 0,005 % p/v, d'au plus 0,003 % p/v, d'au plus 0,002 % p/v ou d'au plus 0,001 % p/v.

7. Composition selon l'une quelconque des revendications 1 à 3, dans laquelle la première fraction se présente sous forme d'unités enrobées.

8. Composition selon la revendication 7, dans laquelle la substance NSAID contenue dans la première fraction a une valeur pK_a d'au moins 5,0, par exemple d'au moins 5,5.

9. Composition selon l'une quelconque des revendications 7 ou 8, dans laquelle la substance NSAID a une solubilité dans de l'acide chlorhydrique 0,1 N à température ambiante d'au moins 0,1 % p/v, par exemple d'au moins 0,5 % p/v ou d'au moins 1 % p/v.

10. Composition selon l'une quelconque des revendications précédentes, destinée à l'administration d'une quantité efficace du point de vue thérapeutique et/ou prophylactique d'une substance NSAID pour obtenir à la fois un début relativement rapide de l'effet thérapeutique et le maintien de la concentration plasmatique thérapeutiquement active sur une période relativement longue, une posologie unitaire de la composition comprenant au moins deux fractions, comme suit :

une première fraction d'unités multiples à libération rapide pour la libération relativement rapide *in vivo* d'une substance NSAID pour obtenir une concentration plasmatique active du point de vue thérapeutique et/ou prophylactique sur une période relativement courte, et
une seconde fraction d'unités multiples modifiées enrobées pour la libération prolongée *in vivo* d'une substance NSAID pour maintenir une concentration plasmatique active du point de vue thérapeutique et/ou proplylactique afin de permettre un dosage une à deux fois par jour,
la formulation des première et seconde fractions, par rapport à leur libération et au rapport entre les première et seconde fractions dans la posologie unitaire étant adapté de façon à obtenir :

une libération *in vitro* relativement rapide de la substance NSAID à partir de la première fraction d'unités multiples à libération rapide, comme cela a été déterminé par la méthode de dissolution II telle que définie ici,
une libération *in vitro* prolongée de la substance NSAID à partir de la seconde fraction d'unités multiples à libération prolongée par rapport à la première fraction à libération *in vitro* de la substance NSAID, comme cela a été déterminé par la méthode de dissolution III telle que définie ici,
la libération rapide et la libération *in vitro* prolongée étant adaptées de manière à ce que la première

fraction soit libérée lorsque la libération de la seconde fraction est commencée, ce qui correspond à au moins 50 % p/p de la substance NSAID contenue dans la première fraction au moment où au moins 15 % p/p, par exemple au moins 10 % p/p ou au moins 5 % p/p de la substance NSAID contenue dans la seconde fraction sont libérés comme cela a été déterminé par la méthode de dissolution III définie ici.

11. Composition selon l'une quelconque des revendications précédentes, dans laquelle la substance NSAID est choisie dans le groupe comprenant les substances suivantes : lornoxicam, diclofénac, nimésulide, ibuprofène, piroxicam, piroxicam (bêtacyclodextrine), naproxène, kétoprofène, ténoxicam, acéclofénac, indométacine, nabumétone, acémétacine, morniflumate, méloxicam, flurbiprofène, acide tiaprofénique, proglumétacine, acide méfénamique, fenbufène, étodolac, acide tolfénamique, sulindac, phénylbutazone, fénoprofène, tolmétine, acide acétylsalicylique, dexibuprofène et des sels pharmaceutiquement acceptables, complexes et/ou promédicaments et des mélanges de ceux-ci.

12. Composition selon l'une quelconque des revendications précédentes, dans laquelle la substance NSAID dans la première fraction est la même que la substance NSAID contenue dans la seconde fraction.

13. Composition selon l'une quelconque des revendications 1 à 11, dans laquelle la substance NSAID dans la première fraction est différente de la substance NSAID contenue dans la seconde fraction.

14. Composition selon l'une quelconque des revendications précédentes, dans laquelle la substance NSAID dans la première fraction est le lornoxicam.

15. Composition selon l'une quelconque des revendications précédentes, dans laquelle la substance NSAID dans la seconde fraction est le lornoxicam.

16. Composition selon l'une quelconque des revendications précédentes, comprenant une autre substance médicamenteuse active.

17. Composition selon l'une quelconque des revendications précédentes, dans laquelle une autre substance médicamenteuse active est incluse dans au moins l'une des première et seconde fractions.

18. Composition selon l'une quelconque des revendications 16 ou 17, dans laquelle l'autre substance médicamenteuse active est choisie dans le groupe comprenant un antidépresseur, un opioïde, un analogue de la prostaglandine, un glucocorticostéroïde, un cytostatique, un antagoniste du récepteur H2, un inhibiteur de pompe protonique et/ou un antiacide.

19. Composition selon l'une quelconque des revendications 16 ou 17, dans laquelle l'autre substance médicamenteuse active est choisie dans le groupe comprenant le paracétamol, la pénicillamine, la sulfasalazine et l'auranorfine.

20. Composition selon l'une quelconque des revendications précédentes, dans laquelle la substance NSAID est le lornoxicam.

21. Composition selon l'une quelconque des revendications précédentes, dans laquelle les unités multiples à libération rapide de la première fraction ont une taille de particules moyenne d'au plus 250 µm, par exemple d'au plus 240 µm, d'au plus 230 µm, d'au plus 220 µm, d'au plus environ 210 µm, d'au plus 200 µm, d'au plus 190 µm, d'au plus 180 µm, d'au plus 175 µm, d'au plus 150 µm, d'au plus 125 µm, d'au plus 100 µm, d'au plus 90 µm ou d'au plus 80 µm.

22. Composition selon l'une quelconque des revendications précédentes, dans laquelle les caractéristiques de dissolution *in vitro* de la première fraction d'unités multiples à libération rapide procurent en moins d'une heure une libération de ladite substance NSAID comme cela a été déterminé par la méthode de dissolution II définie dans la présente d'au moins 50 % p/p, par exemple d'au moins 60 % p/p, d'au moins 70 % p/p, d'au moins 80 % p/p, d'au moins 85 % p/p, d'au moins 90 % p/p ou d'au moins 95 % de la substance NSAID.

23. Composition selon l'une quelconque des revendications précédentes, dans laquelle les caractéristiques de dissolution *in vitro* de la seconde fraction d'unités multiples à libération prolongée procurent en moins d'une heure une libération comme cela a été déterminé par la méthode de dissolution III définie dans la présente, dans la plage de 0 % à 30 % p/p, par exemple dans la plage de 0 % à 20 % p/p, dans la plage de 0 % à 10 % p/p, par exemple

d'au plus 5 % p/p de la substance NSAID.

24. Composition selon l'une quelconque des revendications précédentes, dans laquelle les caractéristiques de dissolution *in vitro* de la seconde fraction d'unités multiples à libération prolongée procurent, en moins de 3 heures, une libération comme cela a été déterminé par la méthode de dissolution III définie dans la présente dans la plage de 10 % à 70 % p/p, par exemple dans la plage de 10 % à 60 % p/p, dans la plage de 12 % à 50 % p/p, dans la plage de 14 % à 45 % p/p, dans la plage de 15 % à 30 % p/p, dans la plage de 15 % à 20 % p/p, par exemple 17 % p/p de la substance NSAID.

25. Composition selon l'une quelconque des revendications précédentes, dans laquelle les caractéristiques de dissolution *in vitro* de la seconde fraction d'unités multiples à libération prolongée procurent en moins de 6 heures une libération comme cela a été déterminé par la méthode de dissolution III définie dans la présente dans la plage de 35 % à 95 % p/p, par exemple dans la plage de 50 % à 90 % p/p, dans la plage de 50 % à 80 % p/p, dans la plage de 50 % à 75 % p/p, dans la plage de 50 % à 60 % p/p, dans la plage de 53 % à 59 % p/p, par exemple 56 % p/p de la substance NSAID.

26. Composition selon l'une quelconque des revendications précédentes, dans laquelle les caractéristiques de dissolution *in vitro* de la seconde fraction d'unités multiples à libération modifiée procurent en moins de 9 heures une libération de ladite substance NSAID comme cela a été déterminé par la méthode de dissolution III définie dans la présente dans la plage de 50 % à 100 % p/p, par exemple comme dans la plage de 60 % à 98 % p/p, dans la plage de 65 % à 95 % p/p, dans la plage de 70 % à 90 % p/p, dans la plage de 70 % à 80 % p/p, par exemple 76 % p/p de la substance NSAID.

27. Composition selon l'une quelconque des revendications précédentes, dans laquelle les caractéristiques de dissolution *in vitro* des première et seconde fractions sont adaptées de telle sorte que la substance NSAID de la première fraction soit libérée lorsque la libération de ladite substance NSAID de la seconde fraction est commencée, ce qui correspond à au moins 50 % p/p de la première fraction au moment où sont libérés au plus 15 % p/p, par exemple au plus 10 % p/p ou au plus 5 % p/p de la substance NSAID dans la seconde fraction, comme cela a été déterminé par la méthode de dissolution III définie ici.

28. Composition selon l'une quelconque des revendications précédentes, dans laquelle les caractéristiques de dissolution *in vitro* des première et seconde fractions sont adaptées de telle sorte que la substance NSAID de la première fraction soit libérée lorsque la libération de ladite substance NSAID de la seconde fraction est commencée, ce qui correspond à au moins 70 % p/p de la libération de la première fraction au moment où sont libérés au plus 20 % p/p de la substance NSAID, par exemple au plus 15 % ou au plus 10 % p/p de la seconde fraction comme cela a été déterminé par la méthode de dissolution III comme cela a été défini ici.

29. Composition selon l'une quelconque des revendications précédentes, dans laquelle les caractéristiques de dissolution *in vitro* de la composition procurent en moins d'une heure une libération de la substance NSAID de la composition, dans la plage de 5 à 50 % p/p, par exemple dans la plage de 5 à 45 % p/p, dans la plage de 15 à 40 % p/p, dans la plage de 20 à 35 % p/p, par exemple 29 % p/p, comme cela a été déterminé par la méthode de dissolution III telle que définie ici.

30. Composition selon l'une quelconque des revendications précédentes, dans laquelle les caractéristiques de dissolution *in vitro* de la composition procurent en moins de 3 heures une libération de la substance NSAID de la composition, comme cela a été déterminé par la méthode de dissolution III telle que définie ici, dans la plage de 20 à 80 % p/p, par exemple dans la plage de 25 à 70 % p/p, dans la plage de 30 à 60 % p/p, dans la plage de 35 à 55 % p/p, par exemple 42 % p/p.

31. Composition selon l'une quelconque des revendications précédentes, dans laquelle les caractéristiques de dissolution *in vitro* de la composition procurent en moins de 6 heures une libération de la substance NSAID, comme cela a été déterminé par la méthode de dissolution III définie dans la présente, dans la plage de 40 à 98 % p/p, par exemple dans la plage de 50 à 95 % p/p, dans la plage de 60 à 90 % p/p, dans la plage de 60 à 85 % p/p, de manière préférée entre toutes, dans la plage de 60 à 83 % p/p, par exemple 69 % p/p.

32. Composition selon l'une quelconque des revendications précédentes, dans laquelle les caractéristiques de dissolution *in vitro* de la composition procurent en moins de 9 heures une libération de la substance NSAID comme cela a été déterminé par la méthode de dissolution III telle que définie dans la présente, dans la plage de 50 à

100 % p/p, par exemple dans la plage de 60 à 99 % p/p, dans la plage de 70 à 98 % p/p, dans la plage de 70 à 97 % p/p, dans la plage de 75 à 96 % p/p, dans la plage de 80 à 96 % p/p, dans la plage de 80 à 85 % p/p, par exemple 83 % p/p.

33. Composition selon l'une quelconque des revendications précédentes, dans laquelle le pourcentage de substance NSAID dans la première fraction se situe dans la plage de 5 % à 50 % p/p, par exemple dans la plage de 10 % à 45 % p/p, dans la plage de 15 % à 45 % p/p, dans la plage de 20 % à 40 % p/p, dans la plage de 25 % à 40 % p/p, dans la plage de 25 % à 35 % p/p, par exemple 30 % p/p par rapport à la quantité totale de substance NSAID dans la composition.

34. Composition selon l'une quelconque des revendications précédentes, dans laquelle le pourcentage de substance NSAID dans la seconde fraction se situe dans la plage de 30 % à 99 % p/p, par exemple dans la plage de 40 % à 98 % p/p, dans la plage de 45 % à 95 % p/p, dans la plage de 50 % à 95 % p/p, dans la plage de 55 % à 85 % p/p, dans la plage de 60 % à 80 % p/p, dans la plage de 60 % à 75 % p/p, dans la plage d'environ 65 % à 75 % p/p, par exemple 70 % p/p par rapport à la quantité totale de substance NSAID dans la composition.

35. Composition selon l'une quelconque des revendications précédentes, dans laquelle les unités multiples de la seconde fraction sont des pastilles enrobées de section transversale sensiblement homogène.

36. Composition selon l'une quelconque des revendications précédentes, dans laquelle les unités multiples de la première fraction sont des pastilles enrobées de section transversale sensiblement homogène.

37. Composition selon l'une quelconque des revendications 6 à 36, dans laquelle la première fraction est constituée d'unités enrobées et l'enrobage n'est pas hydrosoluble, mais qui est un enrobage pouvant diffuser dans l'eau et indépendant du pH.

38. Composition selon l'une quelconque des revendications précédentes, dans laquelle une posologie unitaire de la composition comprend de 1 à 32 mg de la substance NSAID.

39. Composition selon l'une quelconque des revendications précédentes, dans laquelle une posologie unitaire comprend de 1 mg à 1,6 g, par exemple de 1 mg à 1,2 g de la substance NSAID.

40. Composition selon l'une quelconque des revendications précédentes, dans laquelle une posologie unitaire comprend de 50 mg à 1,1 g de la substance NSAID.

41. Composition selon l'une quelconque des revendications précédentes, dans laquelle une posologie unitaire comprend de 100 mg à 1,0 g de la substance NSAID.

42. Composition selon l'une quelconque des revendications précédentes, dans laquelle une posologie unitaire comprend de 200 mg à 900 mg de la substance NSAID.

43. Composition selon l'une quelconque des revendications précédentes, dans laquelle une posologie unitaire comprend de 300 mg à 800 mg de la substance NSAID.

44. Composition selon l'une quelconque des revendications précédentes, dans laquelle la posologie unitaire de la composition se présente sous forme d'une gélule, d'un comprimé ou d'un sachet.

45. Composition selon l'une quelconque des revendications précédentes, dans laquelle la substance NSAID est le lornoxicam et la posologie unitaire de la composition contient 4, 8, 12, 16, 20, 24, 28, 32 ou 36 mg de lornoxicam.

46. Composition selon l'une quelconque des revendications précédentes, comprenant au moins 100 unités multiples.

47. Composition selon l'une quelconque des revendications précédentes, dans laquelle la première fraction d'unités multiples se présente sous forme de granules.

48. Procédé pour la préparation d'une forme posologique unitaire d'une composition pharmaceutique orale à libération modifiée comprenant les étapes consistant à :

i) fournir une première fraction d'unités multiples à libération rapide pour une libération relativement rapide *in vivo* d'une substance NSAID, dans lequel ladite fraction comprend une substance antiacide ou un agent alcalin et dans lequel ladite libération rapide *in vitro* étant telle que lorsque l'on soumet la première fraction contenant une substance NSAID à la méthode de dissolution II utilisant du HCl 0,07 N comme milieu de dissolution, au moins 50 % p/p de la substance NSAID est libérée pendant les 20 premières minutes du test ;
ii) fournir une seconde fraction d'unités multiples enrobées à libération prolongée pour la libération prolongée *in vivo* d'une substance NSAID, où lesdites unités enrobées comprennent un enrobage qui n'est pas hydrosoluble, mais qui peut diffuser dans l'eau et qui est indépendant du pH ;
iii) combiner et formuler les première et seconde fractions en ce qui concerne leur libération et en ce qui concerne le rapport entre les première et seconde fractions, de telle sorte que la première fraction soit libérée lorsque la libération *in vitro* de la seconde fraction est commencée, ce qui correspond à une libération d'au moins 50 % p/p de la substance NSAID contenue dans la première fraction au moment où sont libérés au plus 15 % p/p, par exemple au plus 10 % p/p ou au plus 5 % p/p de la substance NSAID contenue dans la seconde fraction comme cela a été déterminé par la méthode de dissolution III telle que défini ici ; et
iv) incorporer dans la forme posologique unitaire au moins lesdites deux fractions i) et ii).

49. Procédé selon la revendication 48, dans lequel la composition est définie selon l'une quelconque des revendications 1 à 47.

50. Utilisation d'une substance médicamenteuse anti-inflammatoire non-stéroïdienne pour la préparation d'un médicament destiné au traitement d'une inflammation et/ou d'une douleur, dans laquelle ledit médicament comprend une composition contenant des unités multiples à libération modifiée sous forme posologique unitaire, ladite forme posologique unitaire comprenant au moins deux fractions contenant la substance NSAID,

i) une première fraction contenant une substance NSAID d'unités multiples pour une libération rapide de la substance NSAID, dans laquelle ladite fraction comprend une substance antiacide ou un agent alcalin, et dans laquelle la libération rapide *in vitro* est telle que, lorsque l'on soumet la première fraction contenant la substance NSAID à la méthode de dissolution II utilisant du HCl 0,07 N comme milieu de dissolution, au moins 50 % p/p de la substance NSAID sont libérés pendant les 20 premières minutes du test ; et
ii) une seconde fraction contenant la substance NSAID d'unités multiples sous la forme d'unités multiples enrobées à libération retardée,

lesdites unités étant enrobées d'un enrobage non hydrosoluble, mais pouvant diffuser dans l'eau et indépendant du pH.

51. Utilisation selon la revendication 50, dans laquelle le médicament comprend une composition selon l'une quelconque des revendications 1 à 47.

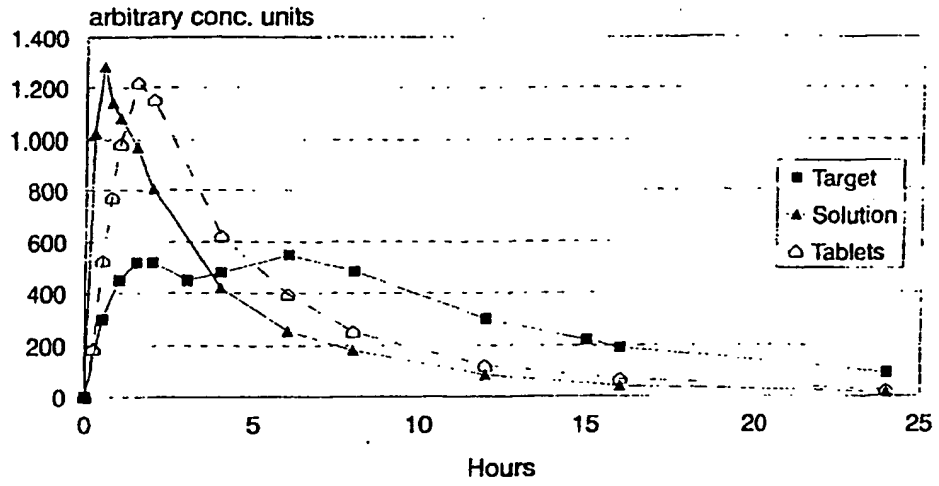
NSAID plasma concentrations
Normalised to same dose
arbitrary conc. units
1.400
1.200
1.000
800
600
400
200
0
0
5
10
15
20
25
Hours
Target
Solution
Tablets

Fig. 1

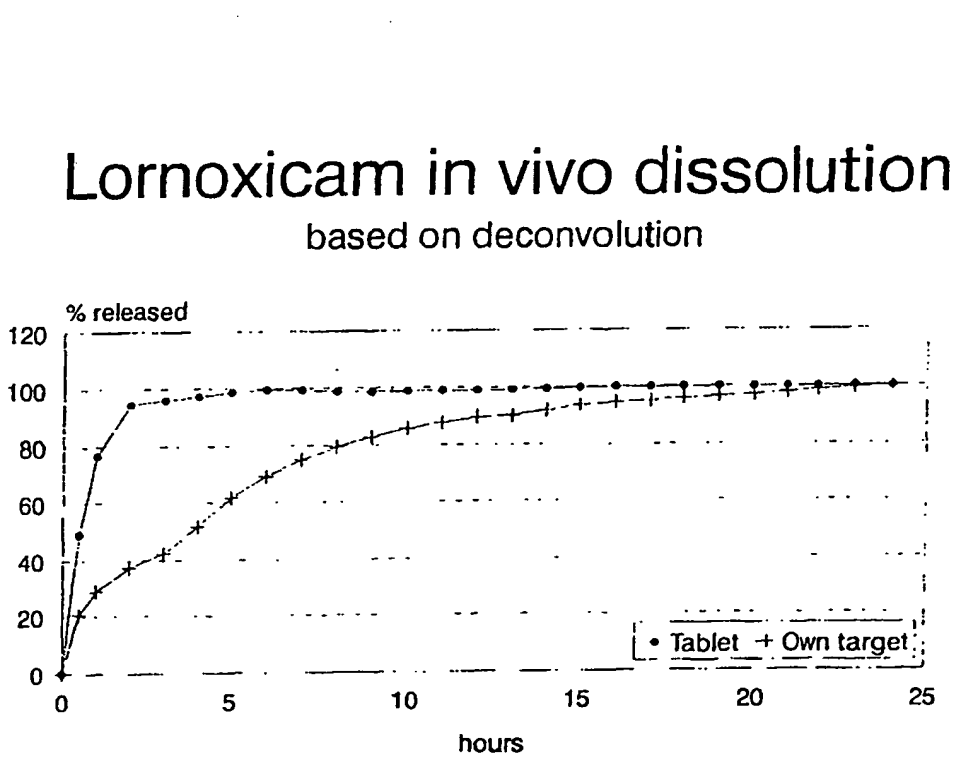
Lornoxicam in vivo dissolution
based on deconvolution
% released
120
100
80
60
40
20
0
0
5
10
15
20
25
hours
Tablet
Own target

Fig. 2

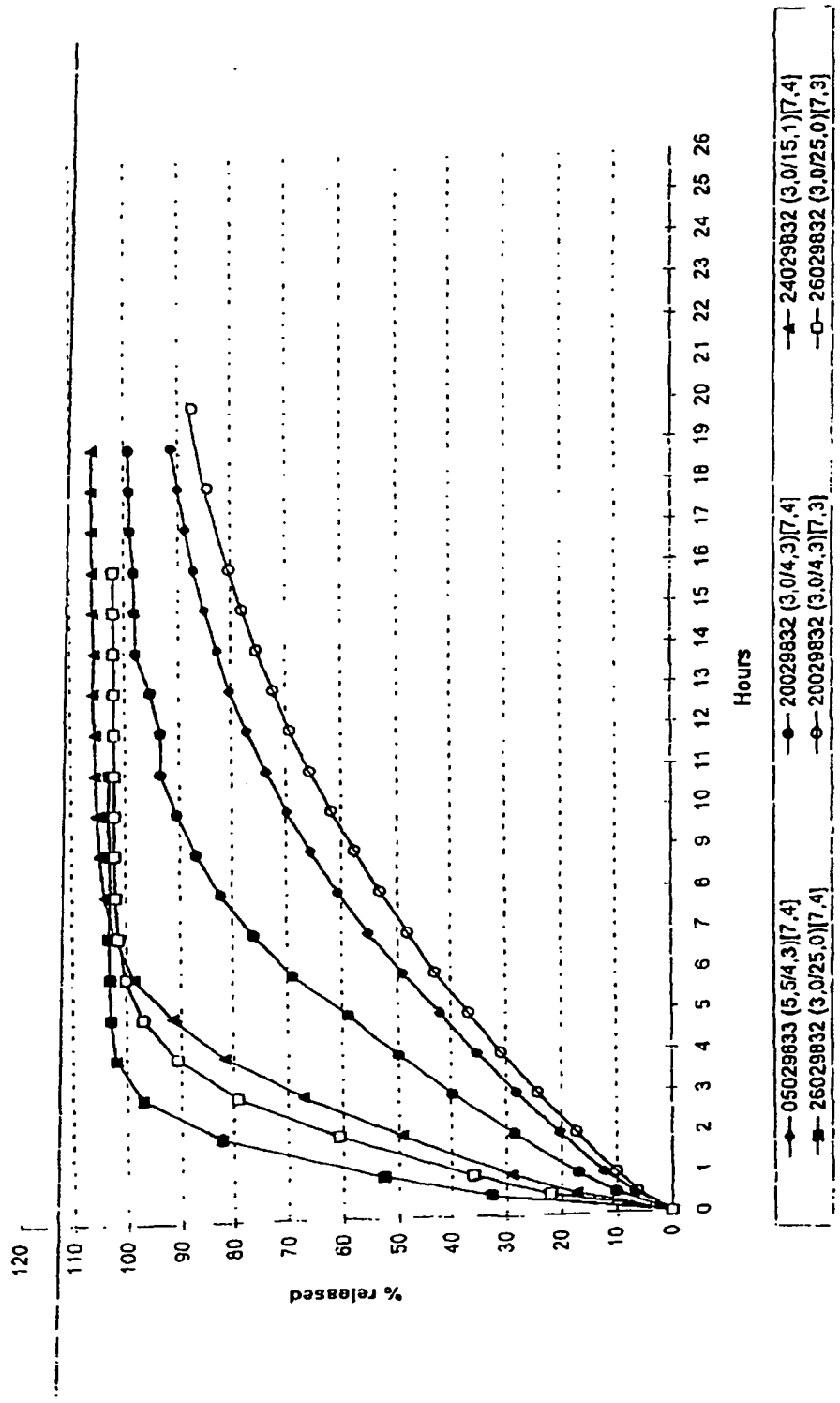
Lornoxicam dissolution, 8 mg
% released
120
110
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Hours
05029833 (5,5/4,3)[7,4]
26029832 (3,0/25,0)[7,4]
20029832 (3,0/4,3)[7,4]
20029832 (3,0/4,3)[7,3]
24029832 (3,0/15,1)[7,4]
26029832 (3,0/25,0)[7,3]

Fig. 3

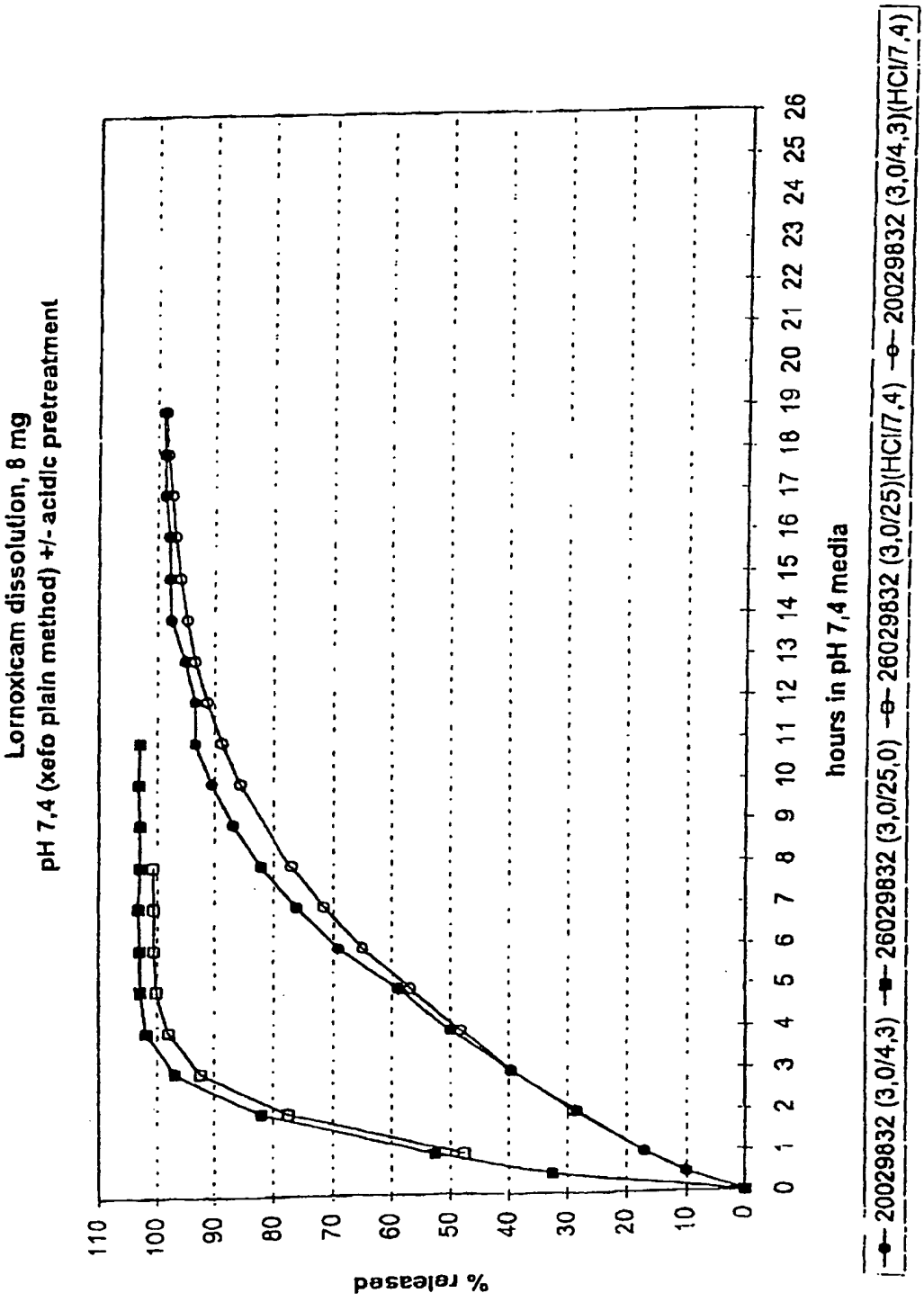
Lornoxicam dissolution, 8 mg
pH 7,4 (xefo plain method) +/- acidic pretreatment
% released
110
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
hours in pH 7,4 media
20029832 (3,0/4,3)
26029832 (3,0/25,0)
26029832 (3,0/25)(HCl/7,4)
20029832 (3,0/4,3)(HCl/7,4)

Fig. 4

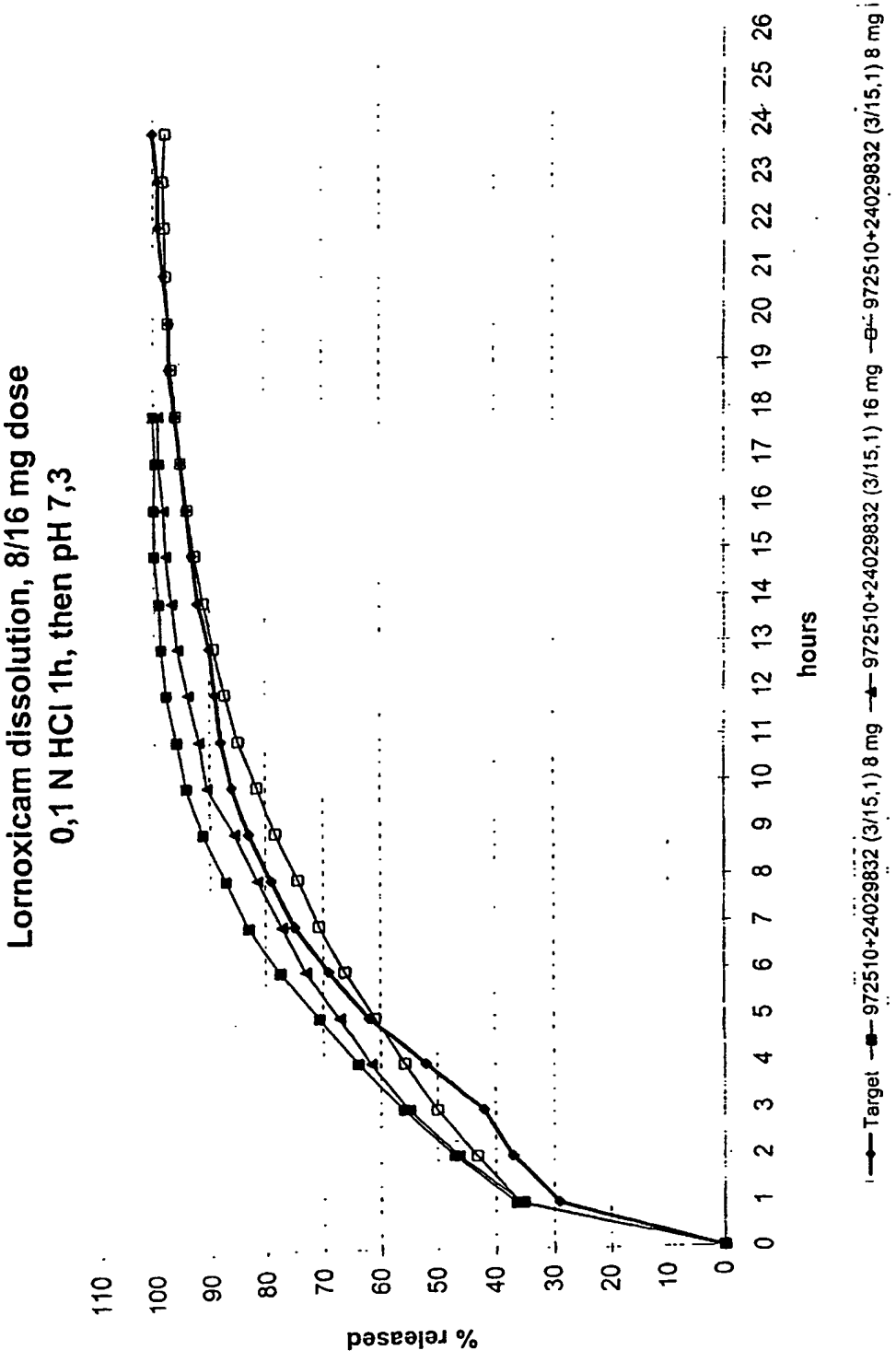
Lornoxicam dissolution, 8/16 mg dose
0,1 N HCl 1h, then pH 7,3
% released
hours
Target
972510+24029832 (3/15,1) 8 mg
972510+24029832 (3/15,1) 16 mg
972510+24029832 (3/15,1) 8 mg

Fig. 5